"A cross sectional study to assess VIRADS score as a diagnostic modality to differentiate between non-muscle invasive and muscle invasive bladder cancer"

Thesis submitted to

The faculty of

All India Institute of Medical Sciences, Bhopal

For the award of the degree of M.Ch in the subject of

Urology

By

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LIST OF ABBREVIATIONS

VIRADS	Vesicle Imaging Reporting and Data System
MIBC	Muscle-invasive bladder cancer
NMIBC	Non-muscle invasive bladder cancer
GLOBOCAN	Global Cancer Observatory
TURBT	Transurethral resection of bladder tumor
T2W	T2- weighted
DWI	Diffusion-weighted (DWI)
DCE	Dynamic gadolinium contrast enhancement
MRI	Magnetic resonance imaging
MpMRI	Multipara metric magnetic resonance imaging
ADC	Apparent diffusion coefficient
BC	Bladder cancer
UC	Urothelial carcinoma
CIS	Carcinoma in-situ
CT	Computed tomography
CTU	Computed tomography urography
SI	Signal intensity
SC	Structural category
CE	Contrast-enhanced
HE	Hematoxylin and eosin
GFR	Glomerular filtration rate

INTRODUCTION

Bladder cancer is ranked 10th among all cancers in the world. In India, as per the GLOBOCON 2018, there were 18,921 new cases and 10,231 deaths with an incidence rate of 2.4 (per 10^5) and 0.7(per $10^{5)}$ in males and females, respectively, and mortality rates of 1.3 (per 10^5) and 0.3(per 10^5), respectively.[1]

Staging of bladder cancer is usually done by clinical examination, histopathological assessment after TURBT, and cross-sectional imaging to assess nodal disease and distant metastasis.[2]

Histologically, the bladder wall is made up of three layers: (a) Mucosa (Urothelial and lamina propria); (b) muscularis propria (detrusor muscle); (c) loose connective tissue and the most common histological type being the Urothelial carcinoma.[2]

Bladder carcinoma is histologically classified into low-grade and high-grade.[3]

Management protocols differ markedly between NMIBC (Ta, T1, or Tis) and MIBC (stage T2 or higher)[2]. NMIBC are treated with TURBT and intravesical instillation. On the other hand, MIBC patients are managed by more intensive therapies like neoadjuvant chemotherapy, radical cystectomy, radiation therapy, and palliative chemotherapy. So, correct staging, by defining the status of muscular layer involvement, is important for the management of bladder cancer.[4]

Cystoscopy with biopsy using transurethral procedures is the gold standard method for defining tumor extension[5]. TURBT is done: (a) to confirm histopathological grade, (b) to determine the depth of tumor invasion, (c) to remove all visible and microscopic tumours.[6]

TURBT is therapeutic in NMIBC and only a preliminary diagnostic step in MIBC or locally advanced disease.[5]

As TURBT is highly operator-dependent, there are chances of residual disease and may miss 25% of invasive cancers.[7] Also, 7-30% NMIBC are under staged after TURBT when resection does not include detrusor muscle, so a second look (Re-TURBT) after 2-6 weeks for all T1 as well as for those with no detrusor muscle was recommended by European Association of Urology Guidelines.[8] The need for repeat TURBT leads to an increase in the cost and complications

associated with treatment and also delays the definitive management in whom it is needed[9]. Also, TURBT carries a risk of bladder perforation and can be a morbidly uncomfortable procedure for the patient.[10]

In this scenario, MRI has proven to be an appropriate tool for staging bladder tumor. Multipara metric MRI, a combination of T2- weighted(T2W), diffusion weighted (DWI) and dynamic gadolinium-enhanced imaging (DCE) sequences provides high tissue contrast resolution to [13]differentiate bladder wall layers.[11] It detects bladder tumor and differentiates superficial lesions from those invading the muscularis propria. And also depicts about the perivesical fat involvement, regional nodal and pelvic metastasis.[9]

Hence, in 2018, bladder mpMRI was released with VIRADS as a standard criteria to discriminate muscle invasion in bladder cancer (which includes the size, location, multiplicity, and morphology of the lesion).[11]This is a 5-point assessment scale classifying the possibility of muscle invasion.[9] It provides anatomical and morphological information on T2 weighted imaging, i.e., evaluates the integrity of muscularis propria; the presence of muscle invasion is decided by DCE, and functional and qualitative information of tissues using DWI. ADC values are complementary in being a functional biomarker independent of morphological features.[12,13] mpMRI helps in accurate tumour detection and staging and can also be used to monitor post-therapy response and identify local recurrence.[13]

This study aims to validate the diagnostic accuracy of the VIRADS scoring system and its individual parameters in detecting bladder muscle invasion in bladder cancer patients. It also aims for high sensitivity and specificity for each score.

The study would try to provide information regarding patients who are diagnosed with bladder masses, whether to undergo mpMRI bladder before undergoing invasive procedures like TURBT or RE-TURBT or to proceed with invasive procedures directly.

As of now literature is not clear for the role of mpMRI in diagnostic workup of bladder cancer, so we did a prospective observational study assess its role.

REVIEW OF LITERATURE

Epidemiology:

Bladder cancer is the 7th most common cancer diagnosed in men globally, though it drops to 10th when both genders are included. The global age-standardized incidence rate is 9.5 per 100,000 for men and 2.4 per 100,000 for women. In India, there were 18,921 new cases and 10,231 deaths. The incidence rate was 2.4 per 100,000 for men and 0.7 per 100,000 for women, while mortality rates were 1.3 and 0.3 per 100,000 for men and women, respectively. India ranks 17th for bladder cancer incidence and 19th for mortality.[14]

From 1989 to 2014, Indian cancer registries showed varied trends. In Delhi, bladder cancer rates rose from 5.2 to 7.4, while Mumbai saw a smaller increase from 3.5 to 4.1. Chennai experienced a decline, from 3.4 to 3.0, and Bangalore remained relatively stable, moving from 2.3 to 2.4.[15]

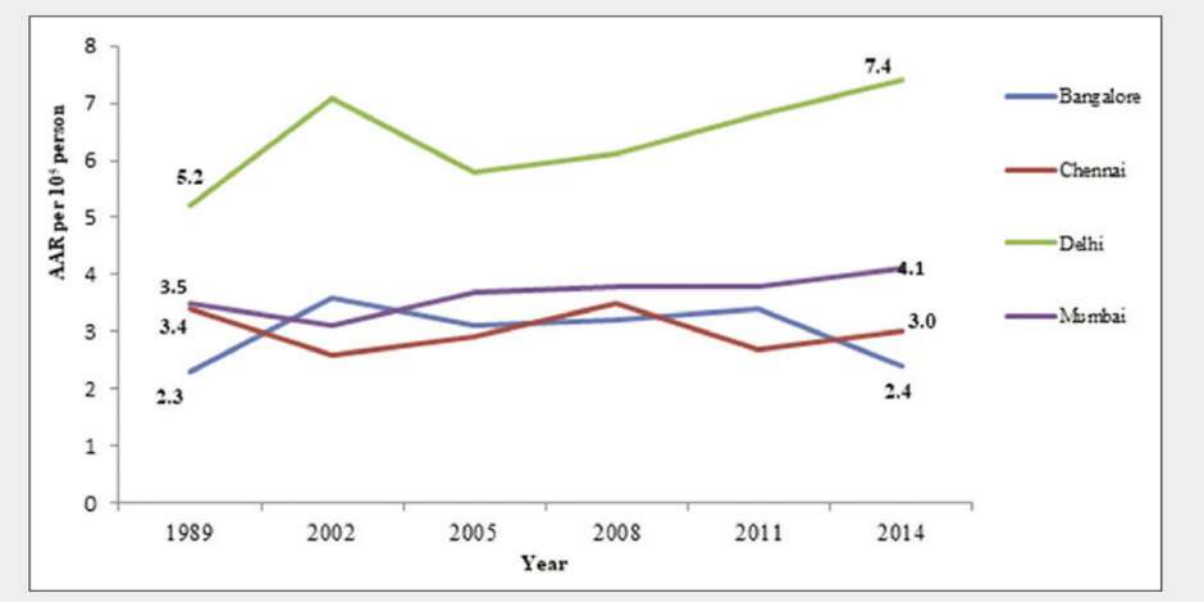


Figure 1- Incidence of bladder cancer in Indian cities[15]

Around 75% of bladder cancer patients present with disease confined to the mucosa (stage Ta, carcinoma in situ [CIS]) or sub mucosa (stage T1). These early-stage patients generally have

better long-term survival rates and lower cancer-specific mortality compared to those with more advanced tumours (T2-T4).[16]

Aetiology

Tobacco Smoking

Smoking is the most significant risk factor for bladder cancer, accounting for 50–65% of cases in men and 20–30% in women.[17]The risk of bladder cancer increases with the duration of smoking and the number of cigarettes smoked.[18]Starting smoking at a young age raises the likelihood of death from bladder cancer, but stopping smoking reduces the risk by about 40% within the first four years and by 60% after 25 years of cessation.[19]

Occupational Exposure

Exposure to certain chemicals, particularly carcinogenic aromatic amines, is the second most important risk factor for bladder cancer. The risk increases significantly after ten years of exposure, with a latency period that can exceed 30 years.[20]

Radiotherapy

In a U.S. population study, bladder cancer risk was elevated after radiotherapy (RT) for prostate cancer, with standardized incidence ratios for external beam radiation therapy (EBRT) and brachytherapy between 1.10 and 1.42. [21]Newer RT techniques like intensity-modulated radiotherapy (IMRT) may reduce the risk of secondary bladder and rectal cancers.[22]

Bladder Schistosomiasis and Chronic Urinary Infections

Schistosomiasis, a parasitic infection, has a well-established link to bladder cancer, particularly squamous cell carcinoma (SCC). However, better disease control has reduced SCC incidence in endemic regions like Egypt[23].Chronic urinary tract infections, distinct from Schistosomiasis, are also associated with an increased risk of invasive squamous cell carcinoma due to chronic inflammation or irritation of the urothelium.[24]

Gender

Men are more likely to develop bladder cancer, but women often present with more advanced stages and have poorer survival rates. A meta-analysis of nearly 28,000 patients showed that women have a worse prognosis after radical cystectomy (RC) compared to men (HR: 1.20).[25] Differences in hormone levels, particularly post-menopausal status, may also contribute to this disparity, as estrogen and androgen levels appear to influence the prevalence of bladder cancer in men and women.[26]

Genetic Factors

Genetic variations, such as in N-acetyltransferase 2 (NAT2) and glutathione S-transferase (GSTM1), affect the metabolism of aromatic amines, increasing bladder cancer risk in individuals exposed to environmental carcinogens, particularly through smoking.[27,28]

Pathology

Grading of muscle-invasive bladder cancer (MIBC) offers little prognostic value, as nearly all MIBC cases are classified as high-grade urothelial carcinomas (UCs).[29] Identification of specific morphological subtypes, however, is crucial for prognosis and treatment decisions. The 2004/2016 World Health Organization (WHO) classifications[30] include several recognized subtypes of UC[31], such as:

- Squamous differentiation
- Glandular differentiation
- Nested pattern
- Micro papillary
- Lymphoepithelioma-like
- Plasmacytoid
- Sarcomatoid/carcinosarcoma

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
	T3a microscopically
	T3b macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
	M1a Non-regional lymph nodes
	M1b Other distant metastasis

Figure 2- Staging of bladder cancer[32]

Diagnostic Evaluation :

Bladder Imaging

Patients with a bladder mass detected by diagnostic imaging should undergo cystoscopy, biopsy, and resection for histopathological evaluation. Given the high specificity of imaging for detecting bladder cancer, those with positive results may proceed directly to rigid cystoscopy and transurethral resection without a diagnostic flexible cystoscopy.[33]

Urinary Cytology

Urinary cytology, the examination of voided urine or bladder washings for cancer cells, has high sensitivity for detecting high-grade tumours or carcinoma in situ (CIS). However, positive results may indicate a tumour anywhere in the urinary tract. Despite limitations due to low cellular yield or conditions like urinary tract infections (UTIs), specificity exceeds 90% for experienced readers.[34, 35]

A standardized reporting system, the 'Paris System' redefining urinary cytology diagnostic categories has been updated in 2022 [36]:

• Adequacy of urine specimens (Adequacy);
• Negative for high-grade UC (Negative);
• Atypical urothelial cells (AUC);
• Suspicious for high-grade UC (Suspicious);
• High-grade UC (HGUC).

Cystoscopy

The diagnosis of bladder cancer is confirmed through cystoscopy and histopathological analysis of resected tissue. Flexible cystoscopy in an outpatient setting is recommended for an initial examination, followed by rigid cystoscopy under anaesthesia for a thorough investigation.[37]Photodynamic diagnosis (PDD) is highly sensitive for detecting CIS, although it is not routinely used.[38]

Transurethral Resection of Invasive Bladder Tumours (TURBT)

The aim of TURBT is to provide a histopathological diagnosis and proper staging. Tumours are resected in separate parts, ensuring the inclusion of bladder muscle for accurate staging. In men, the risk of urethral or ductal involvement is higher when the tumour is located at the trigone or bladder neck[39.]

Imaging for Staging of MIBC

CT Imaging

CT is helpful for identifying advanced disease, such as invasion into perivesical fat (T3b) and adjacent organs, though it has limited accuracy for earlier stages[40]. Sensitivity increases as the disease progresses.[41]

Computed tomography urography for local staging of the upper tract, CTU has the highest diagnostic accuracy of the available imaging techniques.[42] the sensitivity of CTU for UTUC is 0.67–1.0 and specificity is 0.93–0.99.[43]

MRI

MRI is more accurate than CT for differentiating between NMIBC and MIBC due to its superior soft tissue contrast.[44] A review of 20 studies found that MRI has a pooled sensitivity of 0.92 and a specificity of 0.88 for distinguishing between stages <T1 and >T2.[45] The VI-RADS system offers a standardized approach to reporting mpMRI for bladder cancer, with high diagnostic accuracy for detecting muscle invasion.[46]

A meta-analysis found that mpMRI with VI-RADS scoring had a pooled sensitivity of 0.83 and specificity of 0.90 for predicting MIBC, with strong inter-reader agreement (with kappa (κ) values ranging from 0.81 to 0.92.[47]

The studies mentioned focus on the application and validation of the Vesicle Imaging-Reporting and Data System (VIRADS) for detecting muscle-invasive bladder cancer (MIBC) using multipara metric MRI (mpMRI).

Panebianco and colleagues (2018) created the VI-RADS score with the aim of standardizing mpMRI reporting and evaluating bladder detrusor muscle invasion. They introduced a five-point scoring system to distinguish between NMIBC and MIBC.[48]

Taguchi et al. found that 18 out of 98 patients were diagnosed with muscle invasion, achieving a 94% accuracy for VIRADS scores ≥ 4.[13]

Wang H and colleagues discovered that a VIRADS score of 3 or higher demonstrated a sensitivity of 87.1% and a specificity of 96.5%. They also observed a significant correlation between VIRADS score and invasion of the bladder muscle.[7]

Del Giudice F et al. confirmed the reliability of VI-RADS in distinguishing between NMIBC and MIBC, with a high sensitivity of 91.9% and specificity of 91.1% during the initial TURBT. They also noted that mpMRI was effective in identifying high-risk NMIBC patients who could potentially avoid Re-TURBT.[50]

Makboul M et al. established a diagnostic accuracy of 84%, with a specificity and negative predictive value (NPV) of 88% for the detection of muscle invasion.[51]

Ghanshyam et al. found that a VIRADS score cut-off of ≥4 achieved a sensitivity of 79.4% and specificity of 94.2%. They also observed that a lower cut-off (≥3) increased sensitivity to 91.2%, but specificity dropped to 78.8%.[52]

Pecoraro et al. (2020) conducted a review of the natural progression of bladder cancer and provided backing for the confirmation of VIRADS for the staging of bladder cancer in various medical facilities.[53]

Yuan B et al. found that they systematically assessed VI-RADS and verified its high diagnostic precision in identifying muscle invasion.[54]

Séguier D et al. found that the combined sensitivity varied from 74.1% to 97.3%, while the specificity ranged from 77% to 100%. This shows that VI-RADS is effective in differentiating between MIBC and NMIBC.[55]

Barchetti G. and colleagues discovered that VIRADS scores greater than 2 were associated with a sensitivity of 91% and 82% for different readers. In addition, scores exceeding 3 enhanced specificity and inter-reader agreement.[10]

Nesrin Gunduz and colleagues showed that when using a VI-RADS cut-off of ≥3, the sensitivity and specificity values were 93.8% and 85.5%, respectively.[56]

Michele Marchioni and colleagues discovered that using VI-RADS score 4 to differentiate between NMIBC and MIBC resulted in a sensitivity of 85.7% and a specificity of 86.9%.[57]

Maha Ibrahim Metwally and colleagues demonstrated that the VIRADS categorization exhibits high diagnostic validity, with outstanding agreement between different readers ($\kappa = 0.93$) and substantial ability to predict muscle invasion following TURBT.[58]

Mustafa Erkoc and colleagues showed that they achieved a high sensitivity of 91.3% and specificity of 91.8% for distinguishing MIBC from NMIBC.[59]

Tarek M El-Karamany and colleagues demonstrated that a VI-RADS score of 3 or higher yielded a sensitivity of 78.6%. Using a cut-off of 2 or higher increased sensitivity but reduced specificity.[60]

Marco Bicchetti and colleagues showed that MRI with VI-RADS ≥3 displayed a high sensitivity (83-93%) and specificity (80-92%) in diagnosing MIBC, with an AUC of 0.95 for experienced readers.[62]

Katerina Rysankova and colleagues found that VI-RADS scores of 3 or higher had a reported sensitivity of 92.3% and specificity of 81.4%. There was a decrease in sensitivity but an increase in specificity for scores of 4 or higher.[63]

Rahul Gupta and colleagues discovered that VI-RADS demonstrated a sensitivity of 95.6% and a diagnostic accuracy of 80.6% in predicting muscle-invasive bladder cancer.[65]

Prateek Gupta et al. stated that the sensitivity and specificity values reported for VI-RADS ≥3 were 94.44% and 87.50%, respectively.[64]

O Kazan et al. found that VIRADS has been validated and demonstrated a sensitivity of 85% and specificity of 80.3% when using a cut-off of ≥3. They also observed a slightly lower sensitivity when using a higher cut-off.[66]

Chayanon Jai-Ua and colleagues used VI-RADS ≥4 to predict muscle invasion.[67]

Naseer UI Islam and colleagues showed high sensitivity (97.56%) and accurate diagnosis (90%) in predicting muscle invasion by using a VI-RADS score of ≥3.[68]

Mrinal Tandon and colleagues found a strong correlation between muscle invasiveness and VIRADS >3, with a sensitivity of 92.31% and specificity of 72.72%.[72]

Mieszko Kozikowski showed that having a VIRADS score of at least 3 is a strong indicator of muscle-invasive bladder cancer, with a high sensitivity of 92% and specificity of 79%.[69]

Christian B van der Pol and colleagues underscored the importance of mpMRI in the local staging of bladder cancer after TURBT, emphasizing its high sensitivity for detecting MIBC.[70]

A study **by Khwaja and colleagues** demonstrated that non-contrast MRI with DWI is highly sensitive in detecting remaining tumors after TURBT and suggested its usefulness in guiding subsequent management.[71]

These studies confirm the efficacy of VIRADS in accurately assessing bladder cancer invasiveness, supporting its widespread use in clinical practice for staging bladder cancer.

AIMS AND OBJECTIVES

Research hypothesis- To assess VIRADS to detect muscle invasion and correctly stage bladder cancer to avoid staging by TURBT.

Aim: To assess mpMRI bladder as a diagnostic modality to differentiate between non-muscle invasive and muscle-invasive bladder cancer.

The primary objective -is to determine the value of mpMRI bladder-vesical imaging reporting and data system (VI-RADS) score for detecting muscle-invasive bladder tumors by comparing it with the histopathological reports.

MATERIAL AND METHODS

Type of study: This is a prospective observational study.

Institute: Department of Urology, AIIMS Bhopal.

Ethical clearance: Ethical clearance was taken from the Institutional Human Ethics Committee (IHEC) of AIIMS, Bhopal.

Study population -This prospective study was conducted from March 2023 to September 2024 on patients suspected to have Urothelial cancer by ultrasonography. Each patient underwent-

Multi-parametric MRI is the combination of a T1-weighted image (T1WI), a high-resolution T2-weighted image (T2WI), and functional imaging techniques, including diffusion-weighted imaging (DWI) and Dynamic contrast-enhanced imaging (DCE).

All patients underwent TURBT after mp-MRI bladder in the urology department AIIMS, Bhopal.

Inclusion Criteria:

All adult patients >18 years of age were admitted to our department with suspected bladder mass on radiological investigation - ultrasonography.

Exclusion criteria:

1. Patients with general contraindications for MRI examination (as metallic implant or pacemaker).
2. Patients with contraindications for transurethral resection (TUR) (as those unfit for surgery).
3. Patients with deranged renal functions, Glomerular filtration rate - 30ml/min/1.73m^2 preventing intravenous administration of contrast agents.
4. Patients with a previous history of chemotherapy for bladder tumors.
5. Patients with a previous history of open surgical procedures for bladder tumors.
6. Patients with a previous history of pelvic radiation.
7. Patients with a history of any endoscopic procedure within two weeks of MRI examination, including previous history of TURBT.
8. TURBT not performed within six weeks of MRI examination.
9. Patients having non-urothelial cell carcinoma variant histology or carcinoma in situ on histopathological examination.

10. Patient with a known history of metastatic bladder cancer.

Study duration: 18 Months

Intervention: Multiparametric MRI of the bladder before TURBT.

Observational protocol:

After assessing for inclusion and exclusion criteria, all patients with suspected bladder mass on the ultrasonography were offered mpMRI before TURBT, after written informed consent.

Timing of MRI:

1. A 2–3-day interval between cystoscopy or Foley catheter removal and MRI examination was kept as per recommendation (To avoid artifacts in imaging).
2. MRI examination was best performed at least 6 wk. before TURBT, bladder biopsy, or intravesical treatment.

Patient preparation:

1. A routine blood investigation including renal function test was done after a detailed history and clinical assessment.
2. Patients was asked to do fasting for 4-6 hours.
3. Depending on the patient's tolerance level, the patient was asked to void 1–2 h before imaging or to start drinking 500–1000 ml of water 30 min before the test. A residual volume ultrasound scan before MRI was used to judge when the bladder is optimally full (around 300 ml) in patients with a history of incomplete bladder emptying. For an under filled bladder, the scan will be repeated in 30–60 min after the patient has drunk more fluid. In case of an overfilled bladder, the patient was asked to partly empty their bladder before the scan was repeated.
4. To reduce bowel peristalsis, an intramuscular antispasmodic agent (20 mg of hyoscine butyl bromide) was administered before the MRI.

Radiological investigations:

All qualified patients underwent a 3 Tesla mpMRI of the bladder, which included T2 weighted images (T2WIs), diffusion-weighted images (DWIs), and dynamic contrast-enhanced images (DCEIs) after confirming that the bladder was adequately distended. T2WIs were captured in three different planes (axial, coronal, and sagittal), DWIs were obtained in the axial plane with

high b values (b=0, 800, 1000, up to 2000 s/mm2), and DCEIs were captured in the axial plane with a temporal resolution of 5s. Each patient received only one VIRADS score. In cases where a patient had multiple bladder lesions, the highest assigned VIRADS score was used. A VIRADS score cut-off of ≥3 was used to identify muscle-invasive tumors. Throughout the procedure, the radiologist was kept informed of the clinical data.

All MRI scans were conducted using 3.0T units (GE) with body array coils. Bladder MR imaging was done in the supine position. DCE imaging of the pelvis will be performed after administration of 0.1 mmol/kg of body weight of gadolinium chelate at a rate of 2 mL/s, followed by administering 20 mL of normal saline to flush the tubing. Images were acquired at multiple phases of contrast medium enhancement in either sagittal or axial oblique planes (pre-contrast and post-contrast at 30 seconds, 60 seconds, 90 seconds, 120 seconds, and 180 seconds).

Table 1-Mpmri bladder image acquisition protocol

Parameter	Sequence	Acquisition plane	TR/TE(Msec)	Acquisition matrix	number of excitations	FOV	Section thickness	b-value (sec/mm2)
T2WI	(2D) fast-spin-echo (FSE) or turbo-spin-echo sequences	Axial, sagittal, coronal	8872/109	260x260	3	17x17cm	3mm	
DWI	Breathing-free spin-echo EPI sequence combined with spectral fat saturation	Axial and sagittal/coronal	6526/80	100x 80	3	20x15cm	4.0mm	800-1000 up to 2000
DCE	3D acquisition LAVA		3.9/1.8	232x192	0.69	32x26cm	4mm	

Assessment for T2W images[73]: Muscle appeared hypo intense on T2W images. This was the first MRI appearance to search in the examination. Interruption of the low SI muscular line suggested muscle invasion. Various situations that existed were:

Structural category (SC) 1: uninterrupted low SI line representing the integrity of muscularis propria (lesion <1 cm; exophytic tumor with or without stalk and thickened inner layer)

SC 2: uninterrupted low SI line representing the integrity of muscularis propria (lesion >1 cm; exophytic tumor with stalk and high SI thickened inner layer, when present, or sessile/broad-based tumor with high SI thickened inner layer, when present)

SC 3: lack of category 2 findings with associated presence of an exophytic tumor without stalk or sessile/broad-based tumor without high SI thickened inner layer but with no clear disruption of low SI muscularis propria

SC 4: interruption of low SI line suggesting an extension of the intermediate SI tumor tissue to muscularis propria

SC 5: extension of intermediate SI tumor to extravesical fat, representing the invasion of the entire bladder wall and extravesical tissues.

Assessment for DCE MRI[73]: As for DCE MRI, the tumor and inner layer enhanced early and may enhance at the same time. Muscularis propria maintained no enhancement in the early phase, and it was recognizable as a low SI line under the tumor. Contrast-enhanced (CE) categories were as follows:

CE category 1: No early enhancement of the muscularis propria (lesions corresponding to SC 1 findings)

CE category 2: no early enhancement of muscularis propria with early enhancement of inner layer (lesions corresponding to SC 2 findings)

CE category 3: lack of category two findings (lesions corresponding to SC category 3 findings) but with no clear disruption of low SI muscularis propria

CE category 4: tumor early enhancement extends focally to muscularis propria

CE category 5: tumor early enhancement extends to the entire bladder wall and extravesical fat

Assessment for DWI/ADC[73]: The tumor was hyper intense on DWI and hypo intense on the ADC map. Muscularis propria may present intermediate SI, while the stalk and inner layer have low SI on DWI.

DW category 1: muscularis propria with intermediate continuous SI on DWI (lesion <1 cm, hyper intense on DWI and hypo intense on ADC, with or without stalk and low SI thickened inner layer on DWI)

DW category 2: muscularis propria with continuous intermediate SI on DWI (lesion >1 cm, hyper intense on DWI and hypo intense on ADC, with low SI stalk and low SI thickened inner layer on DWI or broad-based/sessile tumor with low/intermediate SI thickened inner layer on DWI)

DW category 3: lack of category 2 findings (lesions corresponding to T2 category 3 findings) but with no clear disruption of low SI muscularis propria.

DW category 4: High SI tumor on DWI and low SI tumor on ADC extending focally to muscularis propria.

DW category 5: High SI tumor on DWI and low SI tumor on ADC extending to the entire bladder wall and extravesical fat.

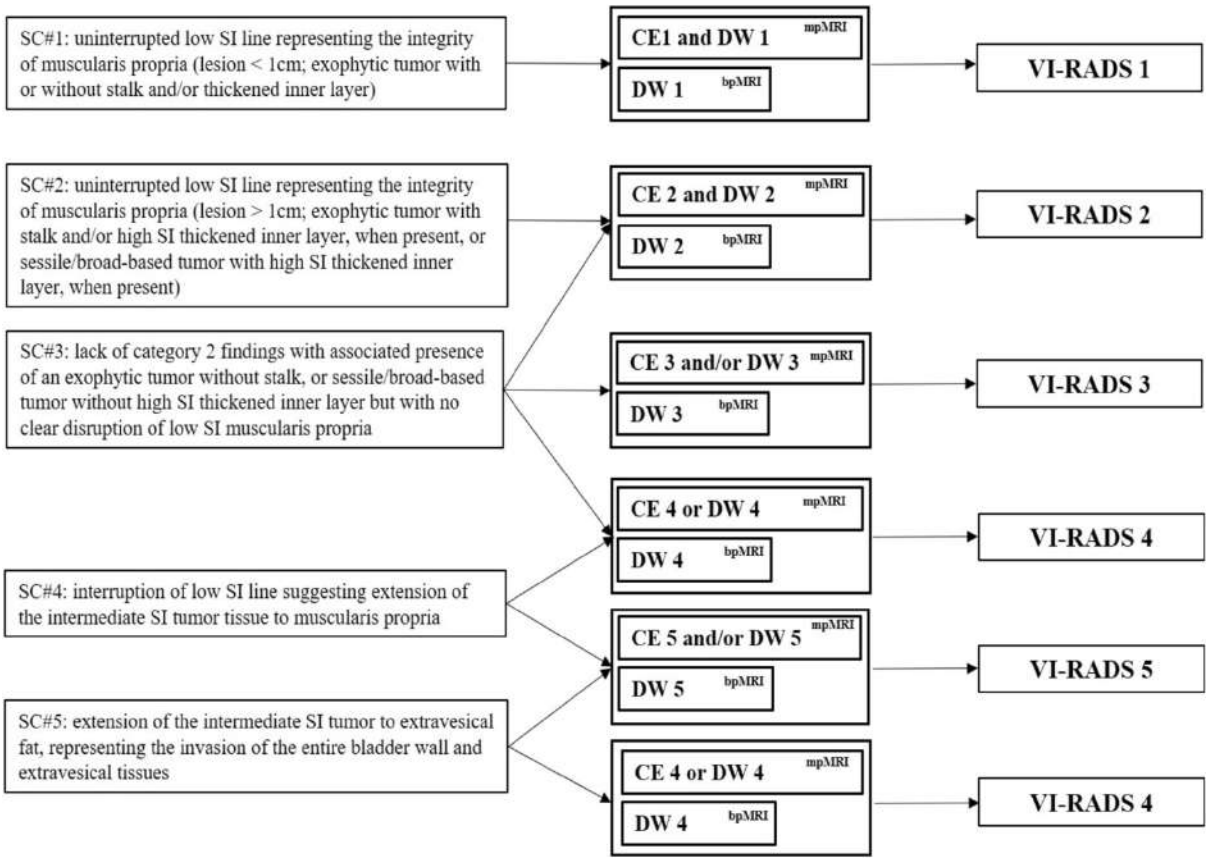


Figure 3: Summary schematic representation of VIRADS scoring.

Scoring interpretation: for categories 1–3, the "first pass scoring" T2 sequence should be considered. For categories 4 and 5, the dominant sequences are DWI (first, when image quality is optimal) and DCE (second). CE = contrast-enhanced category; DCE = dynamic contrast enhancement; DW = diffusion-weighted category; DWI = diffusion-weighted imaging; SC = structural category; SI = signal intensity.

VIRADS category[73]:

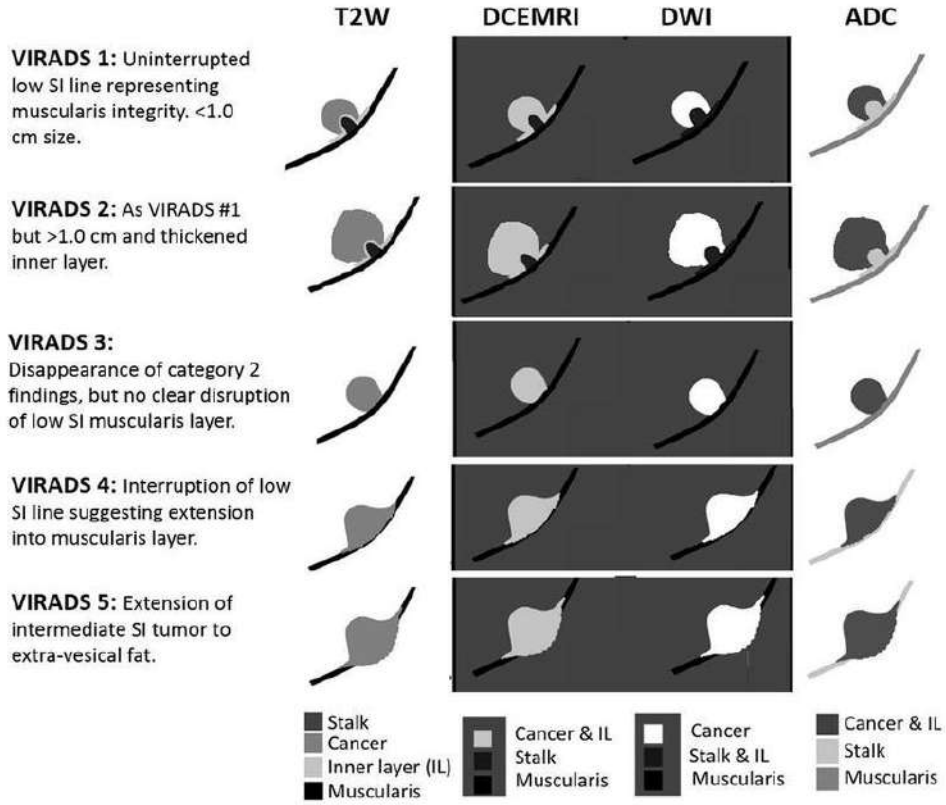
VIRADS 1 (muscle invasion was highly unlikely): SC, CE, and DW category 1

VIRADS 2 (muscle invasion was unlikely to be present): SC, CE, and DW category 2; both CE and DW category 2 with SC category 3

VIRADS 3 (the presence of muscle invasion was equivocal): SC, CE, and DW category 3; SC category 3, CE or DW category 3, the remaining sequence category 2

VIRADS 4 (muscle invasion was likely): at least SC and DW and CE category 4; the remaining category 3 or 4; SC category three plus DW and CE category 4; SC category 5 plus DW and/or CE category 4

VIRADS 5 (invasion of muscle and beyond the bladder was very likely): at least SC plus DW and CE category 5; the remaining category 4 or 5.



<u>Figure 4</u>-Schematic illustration of mpMRI appearances of VIRADS scores 1–5 using T2, DCE MRI, DWI, and ADC weighted images.

ADC = apparent diffusion coefficient; DCE = dynamic contrast enhancement; DWI = diffusion-weighted imaging; SI = signal intensity.(73)

According to VIRADS, a cutoff of ≥3 was used to define MIBC. TURBT reports were compared with preoperative VIRADS scores to assess the accuracy of mpMRI for discriminating between NMIBC and MIBC.

Histopathological Analysis:

Patients received cystoscopy along with TURBT. The surgeon performing the operation observed the following: the number, location, and size of the lesions, the characteristics of the tumor (papillary and sessile), and the condition of the remaining bladder mucosa. If multiple lesions were present, the size of the largest lesion was noted. Additionally, a separate deep biopsy was taken from the base of the tumor. All biopsy samples, including the deep biopsy, were

appropriately labeled, and sent in separate containers to the pathology department for histopathological examination.

For all patients, the tumor's location, stage, muscle invasion, and histologic grade were determined using step-section histologic slices from TURBT. The urologist also documented the location of each removed tumor using a sector map, which was referenced during the histopathological analysis. Patients with non-muscle invasive tumors (T1) following HPE underwent a repeat TURBT (Re-TURBT) after 4 weeks for the final histopathology report.

All tumors were stratified into a low grade (LG) and high-grade (HG) and were evaluated by the 2004/2016 World Health Organization classification:[30]

Ta: Noninvasive papillary carcinoma

Tis: Carcinoma in situ

T1: Tumor invades lamina propria

T2: Tumor invades muscularis propria and higher.

T3: into the layer of fatty tissue that surrounds the bladder (T3a or T3b)

T4: tumor spread into the prostate, uterus, or vagina or growing into the pelvic or abdominal wall.

STATISTICAL ANALYSIS

The information was encoded and documented using the MS Excel spreadsheet application. Data analysis was conducted with SPSS v23 (IBM Corp.). Descriptive statistics were used to present means/standard deviations and medians/IQRs for continuous variables, and frequencies and percentages for categorical variables. Graphical representations, such as histograms for continuous data and bar charts/pie charts for categorical data, were used for data visualization. Group comparisons for categorical data were made using the Chi-squared test, and in cases where the expected frequency in the contingency tables was <5 for more than 20% of the cells, Fisher's Exact test was used instead. A p-value <0.05 was considered significant. On Shapiro wilk test, normality of distribution was assessed. ROC analysis was carried out to determine an optimal cutoff for a continuous predictor in predicting a binary outcome. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy were calculated to assess the diagnostic performance of predictors, utilizing a 2x2 cross-table with the outcome.

RESULTS

FLOW DIAGRAM:

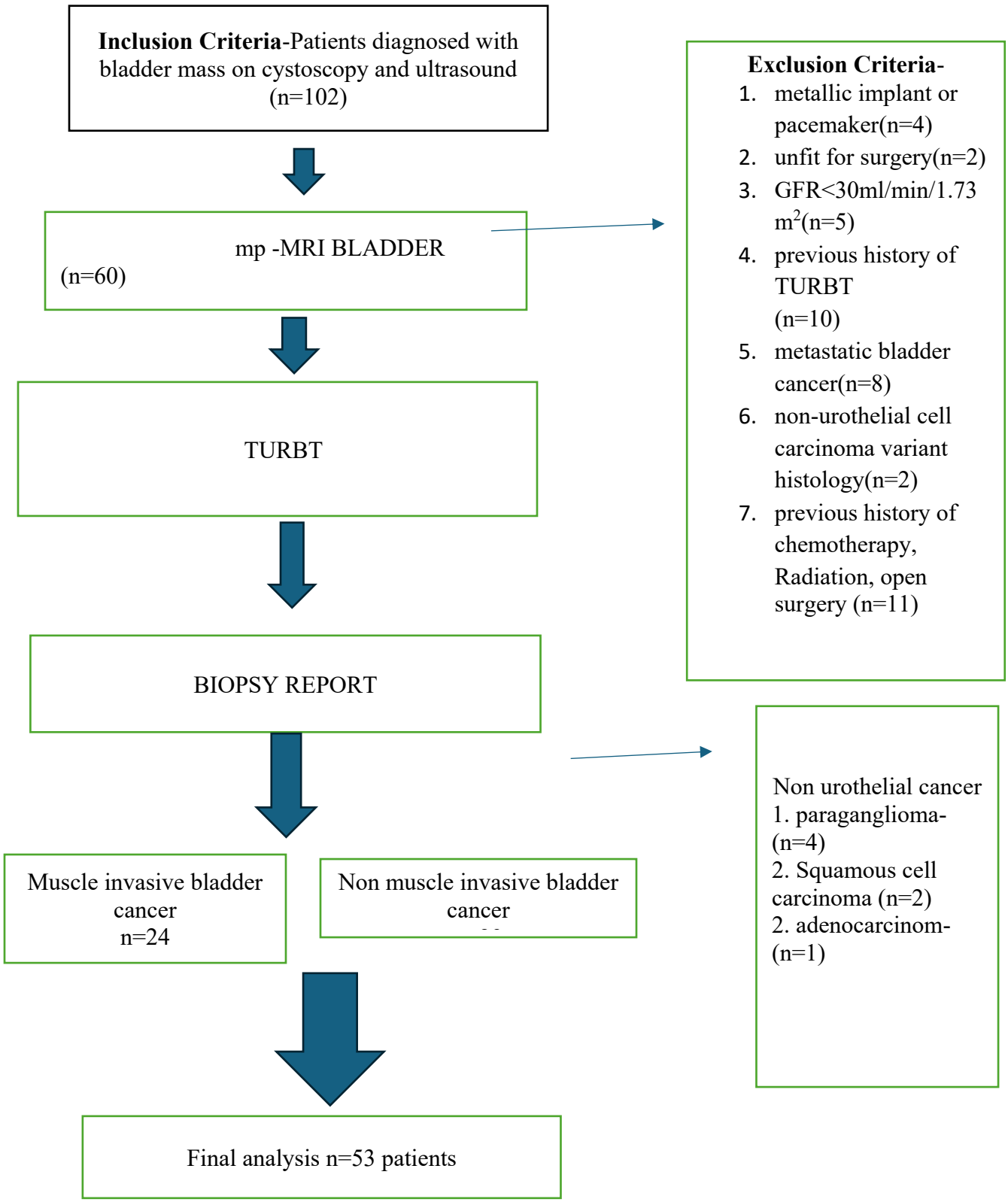

Inclusion Criteria-Patients diagnosed with bladder mass on cystoscopy and ultrasound (n=102)
mp -MRI BLADDER (n=60)
TURBT
BIOPSY REPORT
Muscle invasive bladder cancer n=24
Non muscle invasive bladder cancer
Final analysis n=53 patients
Exclusion Criteria-
1. metallic implant or pacemaker(n=4)
2. unfit for surgery(n=2)
3. GFR<30ml/min/1.73 m^2(n=5)
4. previous history of TURBT (n=10)
5. metastatic bladder cancer(n=8)
6. non-urothelial cell carcinoma variant histology(n=2)
7. previous history of chemotherapy, Radiation, open surgery (n=11)
Non urothelial cancer
1. paraganglioma-(n=4)
2. Squamous cell carcinoma (n=2)
2. adenocarcinom-(n=1)

Figure 5-Flow chart of study design:

The study conducted in our institute enrolled a total of 102 patients who were diagnosed with bladder mass on radiological investigations. Many patients (n=42) were excluded from our study because of metallic implant or pacemaker (n=4), unfit for surgery (n=2), deranged renal function (n=5), previous history of TURBT (n=10), metastasis (n=8), non-urothelial cell carcinoma variant histology (n=2) and prior history of chemotherapy, radiation, open surgery (n=11). Participants who underwent mp-MRI bladder (n=60), seven patients were further excluded due to the nonurothelial variant of bladder cancer on the final histopathology report. The final study population consisted of 24 patients who were diagnosed with Muscle-invasive bladder cancer and 29 with non-invasive bladder cancer, who finally underwent analysis.

Distribution of the participants in terms of 'Age (Years)'

Age (Years)	
Mean (SD)	62.15 (12.52)
Median (IQR)	61 (55-72)
Range	23 – 84

Table 2- Age distribution

The mean (SD) Age (Years) was 62.15 (12.52). The median (IQR) age (Years) was 61.00 (55-72). The Age (Years) ranged from 23 to 84.

The data's sleekness was -0.49, which suggested that it was not skewed and was, therefore, normally distributed. The data's kurtosis was 0.28, suggesting it was normally distributed. The Shapiro-Wilk test for the data was not significant (p = 0.246), suggesting that the data was normally distributed. There appeared to be only one mode/peak in the data, thus making it unimodal.

Since all three criteria (skewness, kurtosis, and Shapiro-Wilk test) suggest normality, the data appeared normally distributed (approximately following a bell-shaped curve).

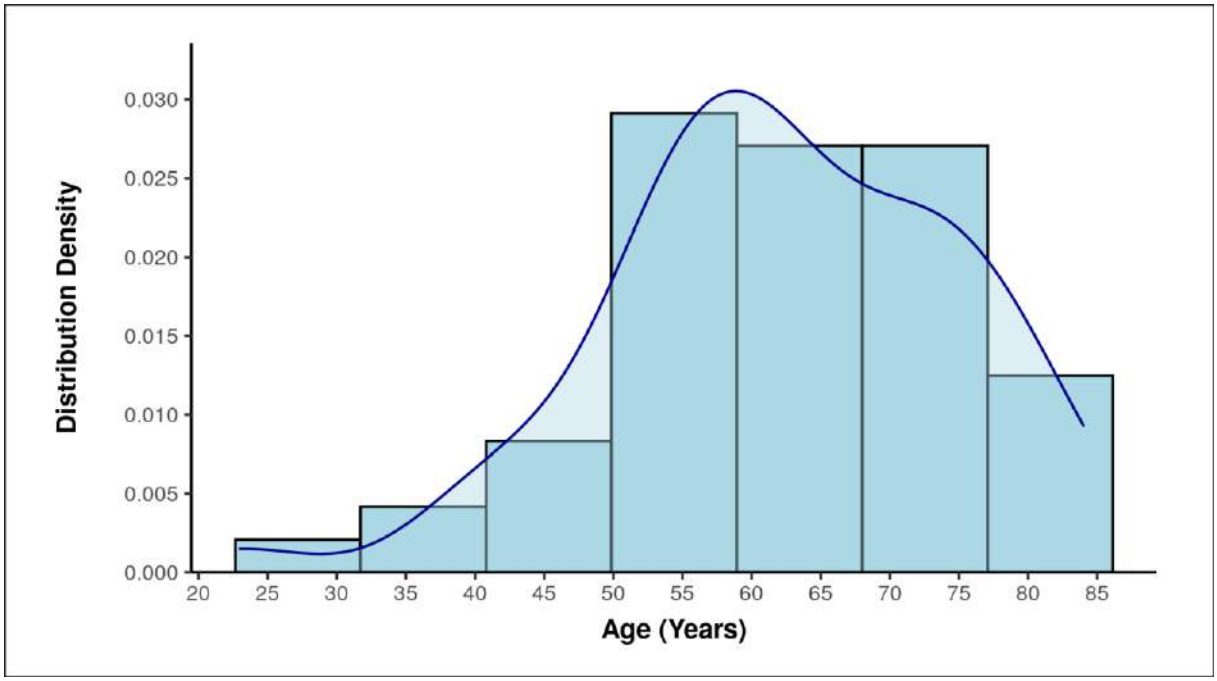


Figure 6: Distribution of age (Years)

The following histogram is plotted with the actual counts, and an ideal bell-shaped curve is superimposed on top for reference:

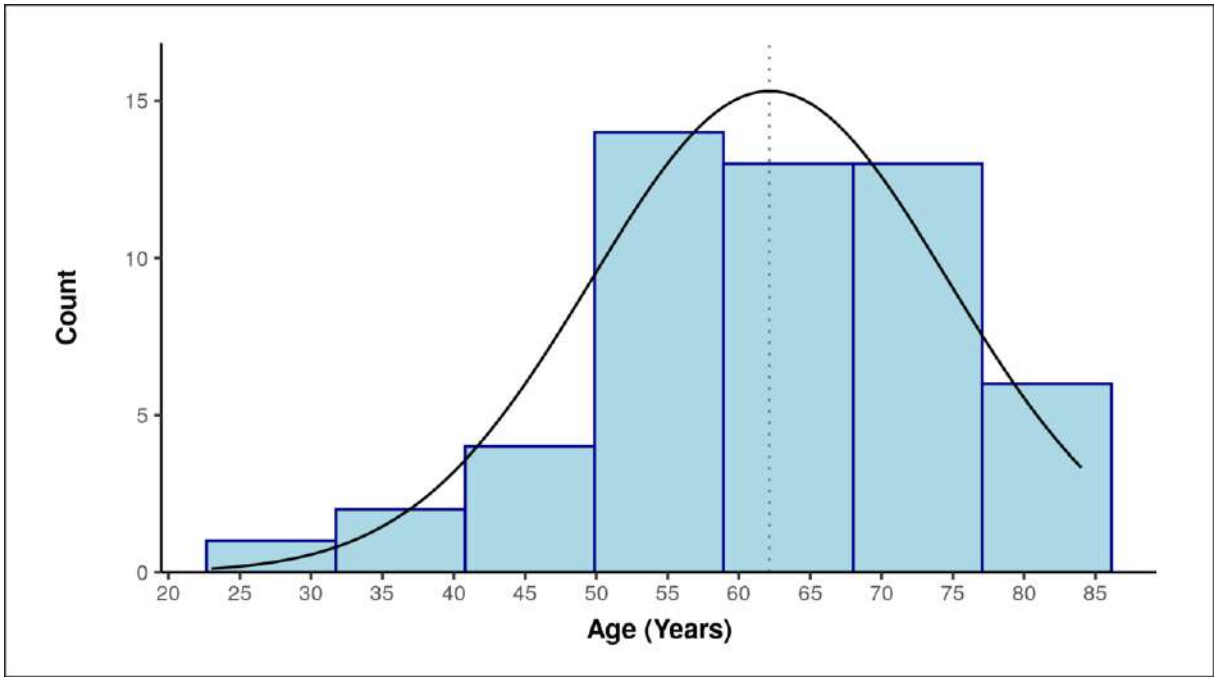


Figure 7: Distribution of age (Years)

Distribution of the participants in terms of 'Gender'

Gender	Frequency	Percentage	95% CI
Male	46	86.8%	74.0% - 94.1%
Female	7	13.2%	5.9% - 26.0%

Table 3- Gender distribution

86.8% of the participants had gender: Male. 13.2% of the participants had gender: Female.

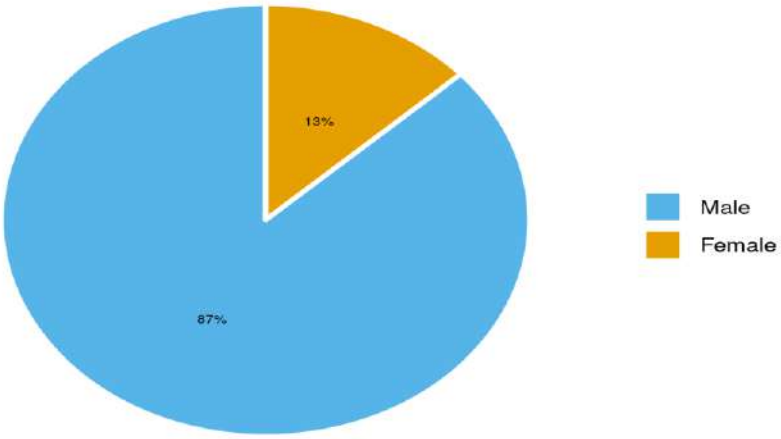


Figure 8: Distribution of Gender

Distribution of the participants in terms of 'VIRADS'

VIRADS	Frequency	Percentage	95% CI
VIRADS 1	3	5.7%	1.5% - 16.6%
VIRADS 2	8	15.1%	7.2% - 28.1%
VIRADS 3	7	13.2%	5.9% - 26.0%
VIRADS 4	16	30.2%	18.7% - 44.5%
VIRADS 5	19	35.8%	23.5% - 50.3%

Table- 4- Distribution of VIRADS

5.7% of the participants had VIRADS 1. 15.1% of the participants had VIRADS 2. 13.2% of the participants had VIRADS 3. 30.2% of the participants had VIRADS 4. 35.8% of the participants had VIRADS 5.

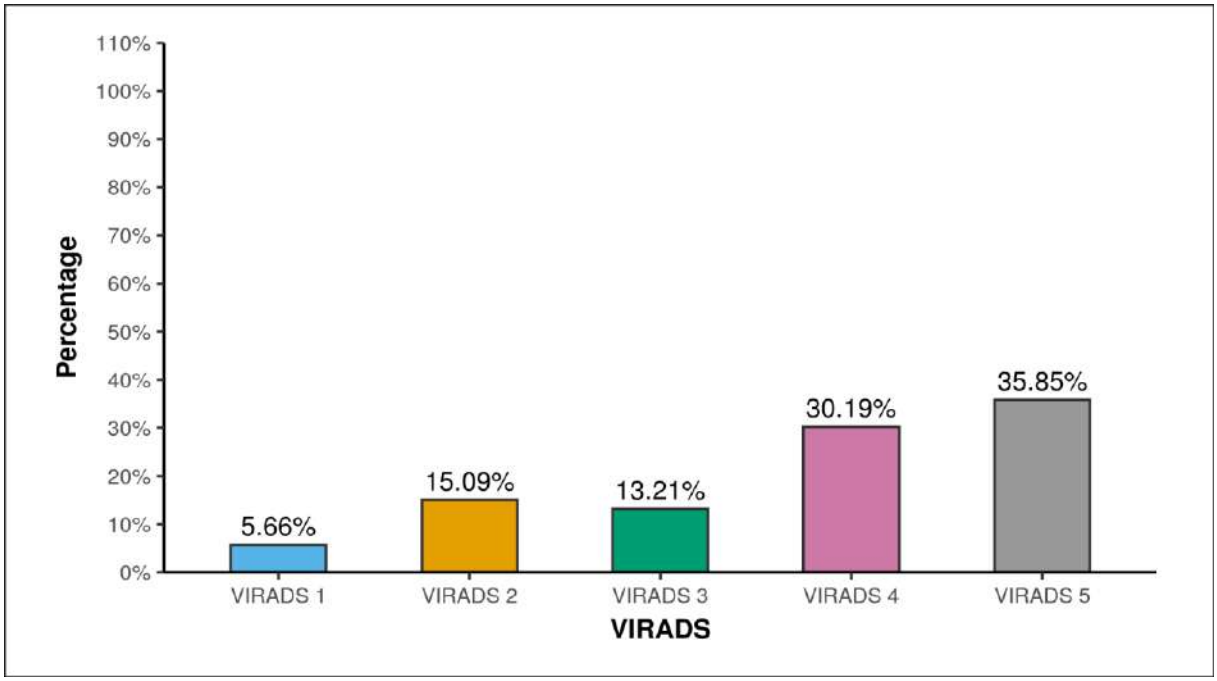


Figure 9: Distribution of VIRADS

Distribution of the participants in terms of 'VIRADS category'

VIRADS Category	Frequency	Percentage	95% CI
VIRADS 1-2	11	20.8%	11.3% - 34.5%
VIRADS 3-5	42	79.2%	65.5% - 88.7%

Table 5- VIRADS category distribution

20.8% of the participants had VIRADS category: VIRADS 1-2. 79.2% of the participants had VIRADS category: VIRADS 3-5.

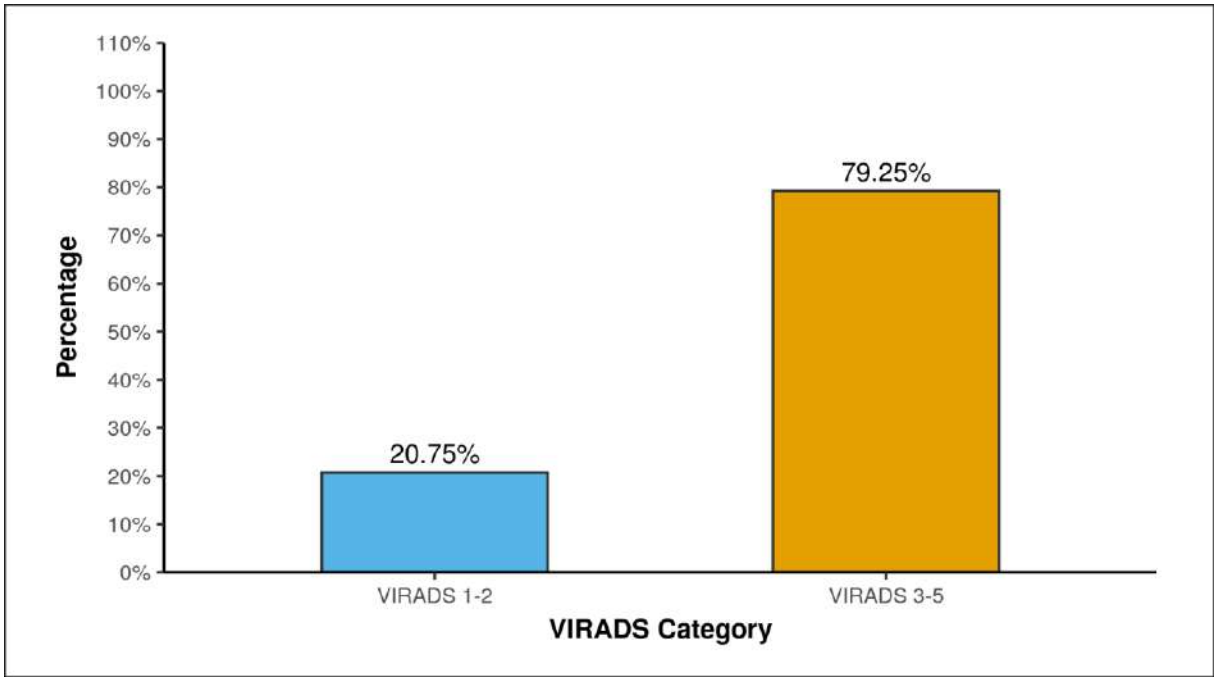


Figure 10: Distribution of VIRADS category

Distribution of the participants in terms of 'Largest Dimensions (cm)'

Largest dimensions (cm)	
Mean (SD)	3.90 (2.33)
Median (IQR)	3.3 (2-5.3)
Range	0.5 - 10.4

Table 6- Size of tumour distribution

The mean (SD) of the largest dimensions (cm) was 3.90 (2.33). The median (IQR) of the largest dimensions (cm) was 3.30 (2-5.3). The largest dimensions (cm) ranged from 0.5 - 10.4.

The skewness of the data was 0.67, suggesting that it was positively skewed and not normally distributed. The kurtosis of the data was -0.07, suggesting that it was normally distributed. The Shapiro-Wilk test for the data was significant (p = 0.025), suggesting that it was not normally distributed. There appeared to be only one mode/peak in the data, thus making it unimodal.

Since only 1 of the 3 criteria (skewness, kurtosis, Shapiro-Wilk test) suggested normality, the data appeared not normally distributed (it did not follow a bell-shaped curve).

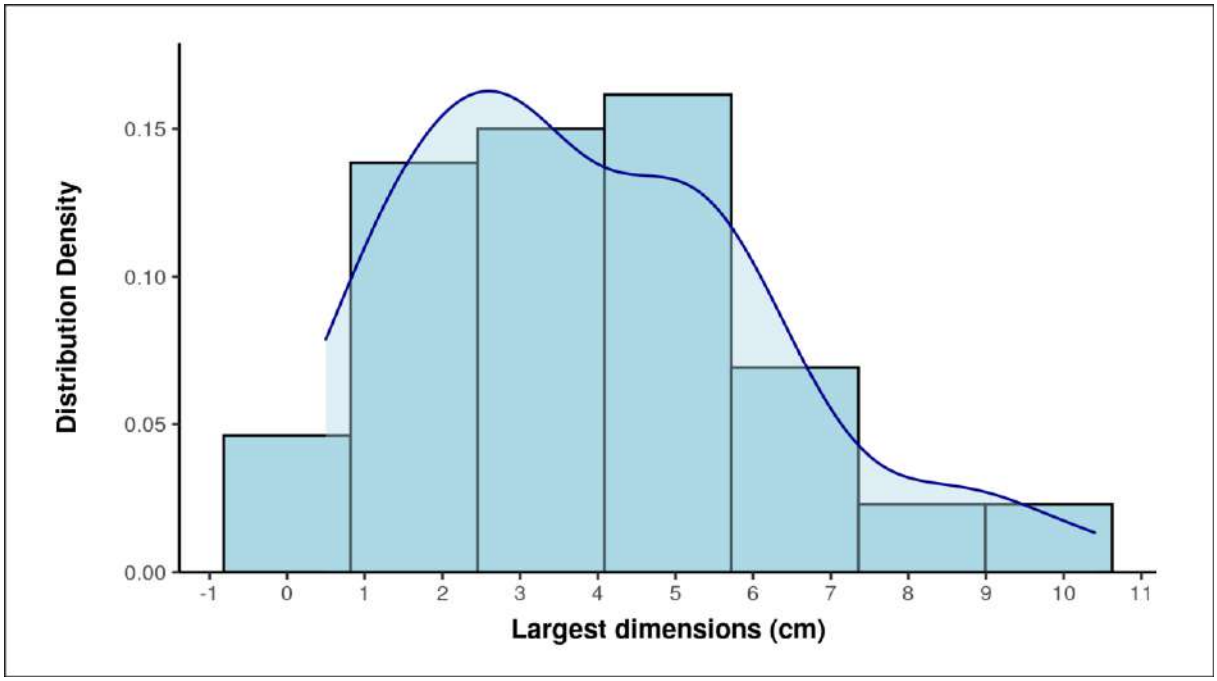


Figure 11: Distribution of largest dimensions (cm)

The following histogram is plotted with the actual counts, and an ideal bell-shaped curve is superimposed on top for reference:

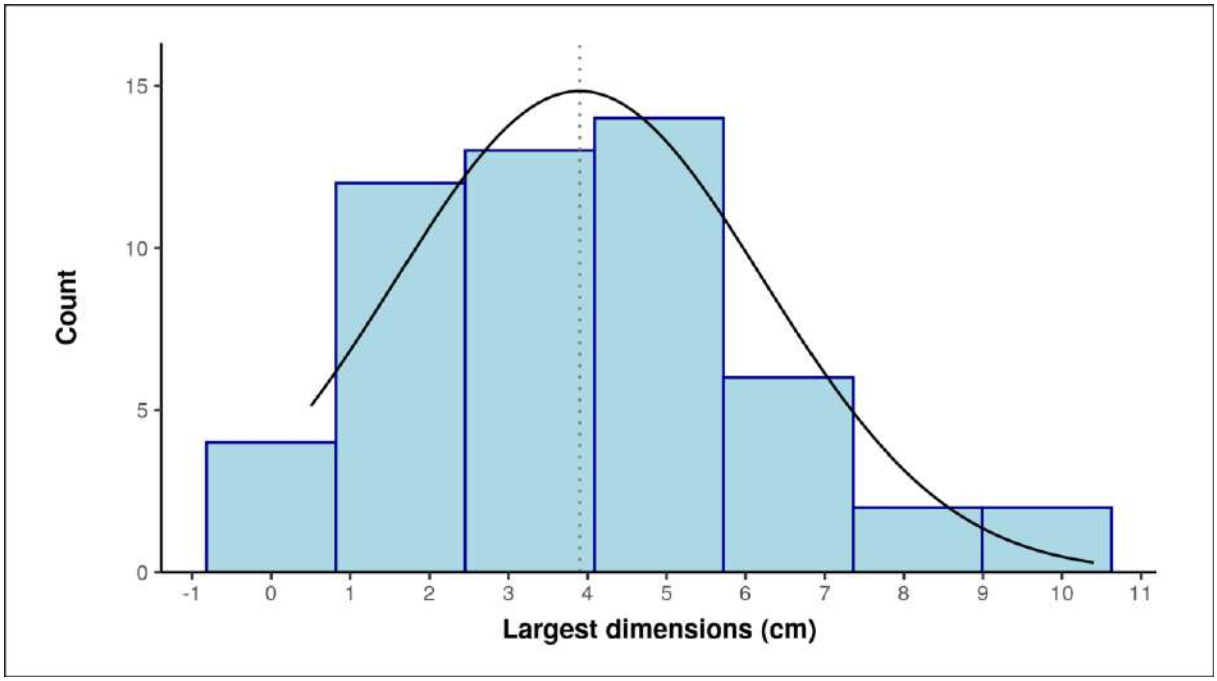


Figure 12: Distribution of largest dimensions (cm)

Distribution of the participants in terms of 'T Stage'

33T Stage	Frequency	Percentage	95% CI
T0	1	1.9%	0.1% - 11.4%
Ta	15	28.3%	17.2% - 42.6%
T1	13	24.5%	14.2% - 38.6%
T2	24	45.3%	31.8% - 59.4%

Table 7- T stage distribution

1.9% of the participants had T Stage: T0, 28.3% had T Stage: Ta, 24.5% had T Stage: T1, and 45.3% had T Stage: T2.

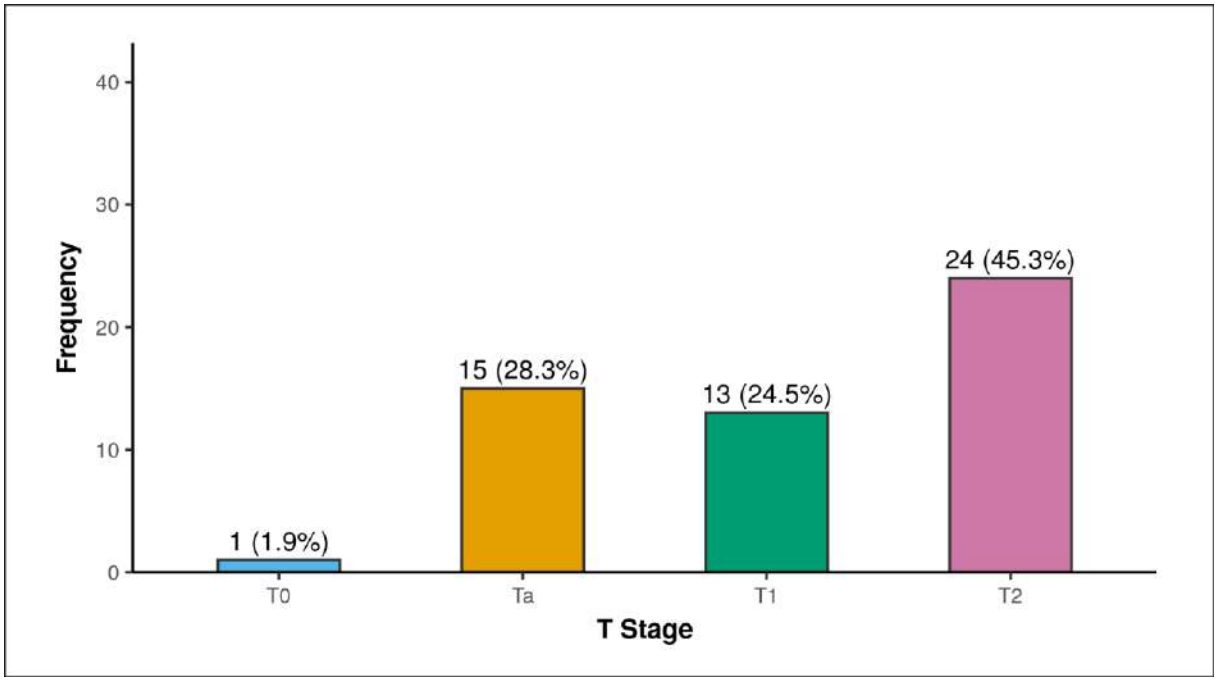


Figure 13: Distribution of T Stage

Distribution of the participants in terms of 'Invasion'

Invasion	Frequency	Percentage	95% CI
Muscle Invasive	24	45.3%	31.8% - 59.4%
Non-Muscle Invasive	29	54.7%	40.6% - 68.2%

Table 8- Distribution in terms of tumour invasion

45.3% of the participants had an invasion that was Muscle-Invasive, and 54.7% had an invasion that was Non-Muscle-Invasive.

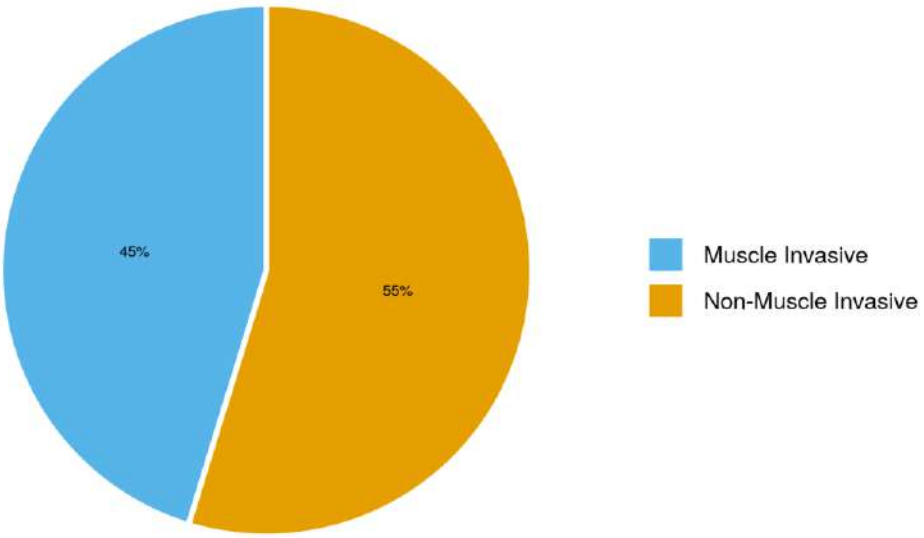


Figure 14: Distribution of in terms of invasion

Distribution of the participants in terms of 'Grade'

Grade	Frequency	Percentage	95% CI
Low	23	44.2%	30.7% - 58.6%
High	29	55.8%	41.4% - 69.3%

Table 9- Distribution in terms of grade

44.2% of the participants had Grade: Low. 55.8% of the participants had a high grade.

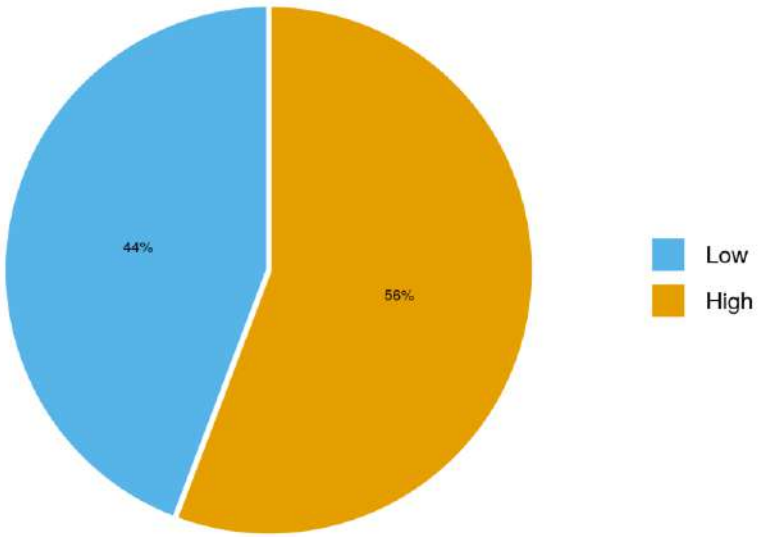


Figure 15: Distribution of in terms of grade

Distribution of the participants in terms of ' Hydronephrosis'

Any Hydronephrosis	Frequency	Percentage	95% CI
Present	13	24.5%	14.2% - 38.6%
Absent	40	75.5%	61.4% - 85.8%

Table 10- Distribution in terms of Hydronephrosis

24.5% of the participants had Hydronephrosis present, and 75.5% had no Hydronephrosis.

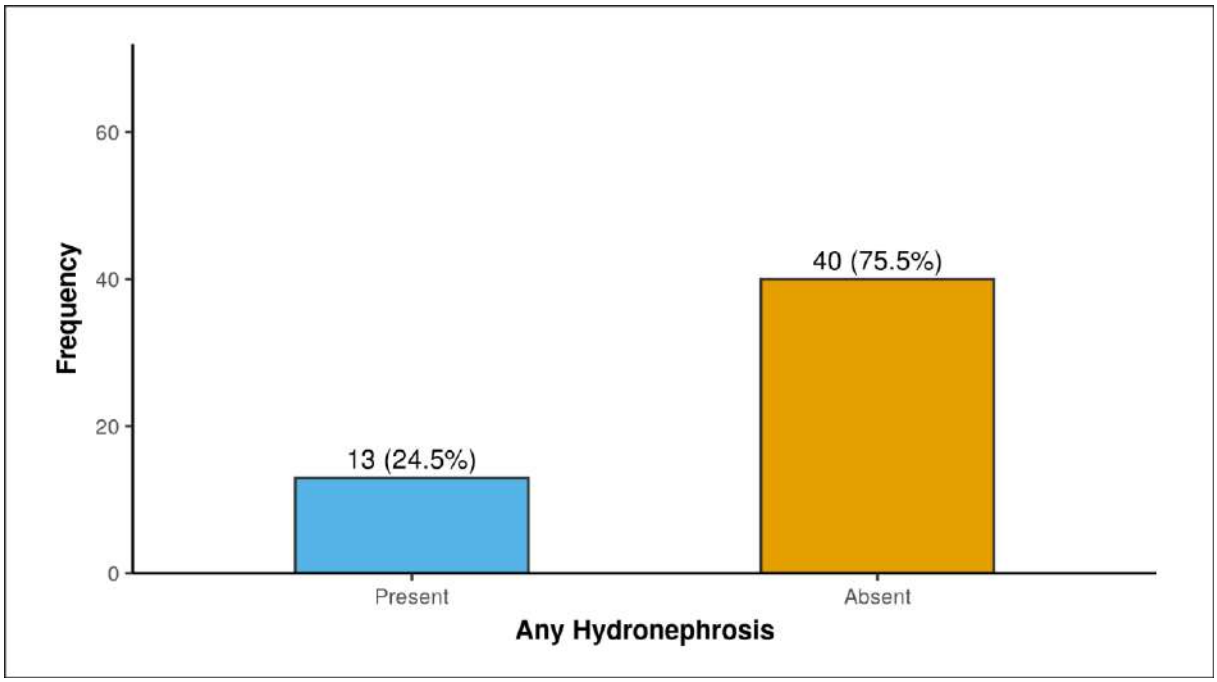


Figure 16: Distribution of in terms of hydronephrosis

Distribution of the participants in terms of 'Hydronephrosis Laterality'

Hydronephrosis Laterality	Frequency	Percentage	95% CI
None	40	75.5%	61.4% - 85.8%
Unilateral	6	11.3%	4.7% - 23.7%
Bilateral	7	13.2%	5.9% - 26.0%

Table 11- Distribution in terms of Hydronephrosis laterality

75.5% of the participants had no Hydronephrosis, 11.3% had unilateral Hydronephrosis and 13.2% had bilateral Hydronephrosis.

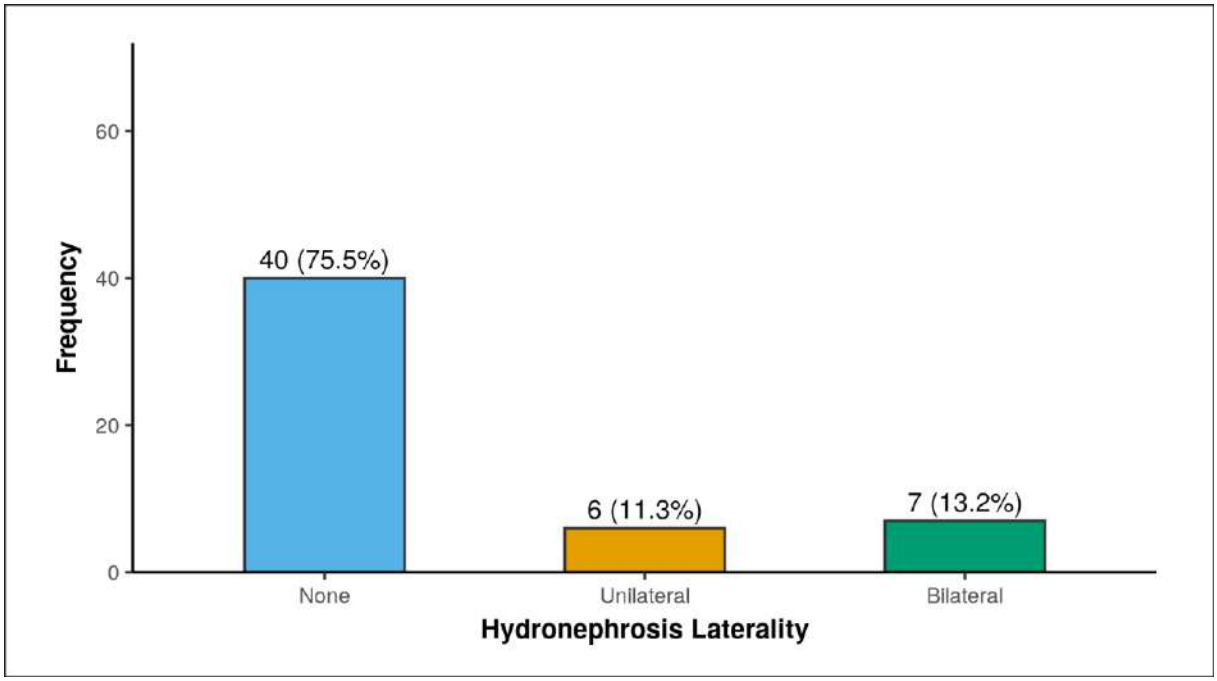


Figure 17: Distribution of Hydronephrosis laterality

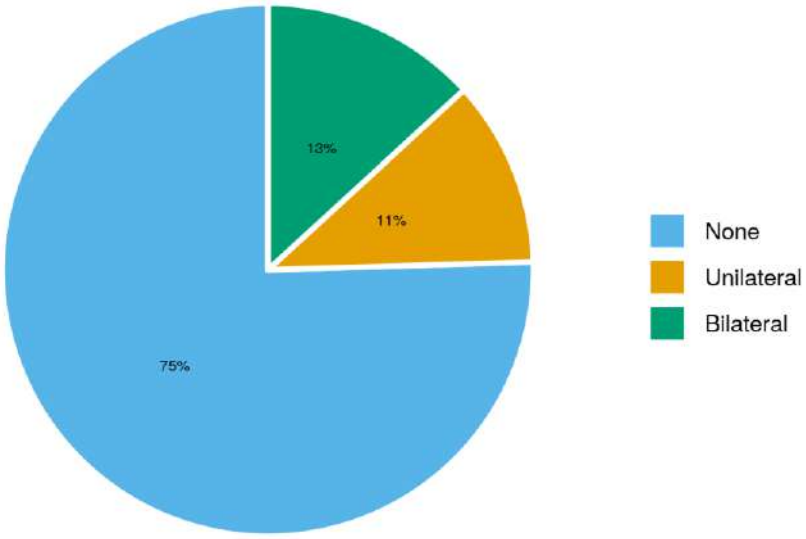


Figure 18: Distribution of Hydronephrosis laterality

Distribution of the participants in terms of 'Lesion Number'

Lesion Number	Frequency	Percentage	95% CI
Single	42	79.2%	65.5% - 88.7%
Multiple	11	20.8%	11.3% - 34.5%

Table 12- Distribution of lesion number

79.2% of the participants had a single lesion, and 20.8% had multiple lesions.

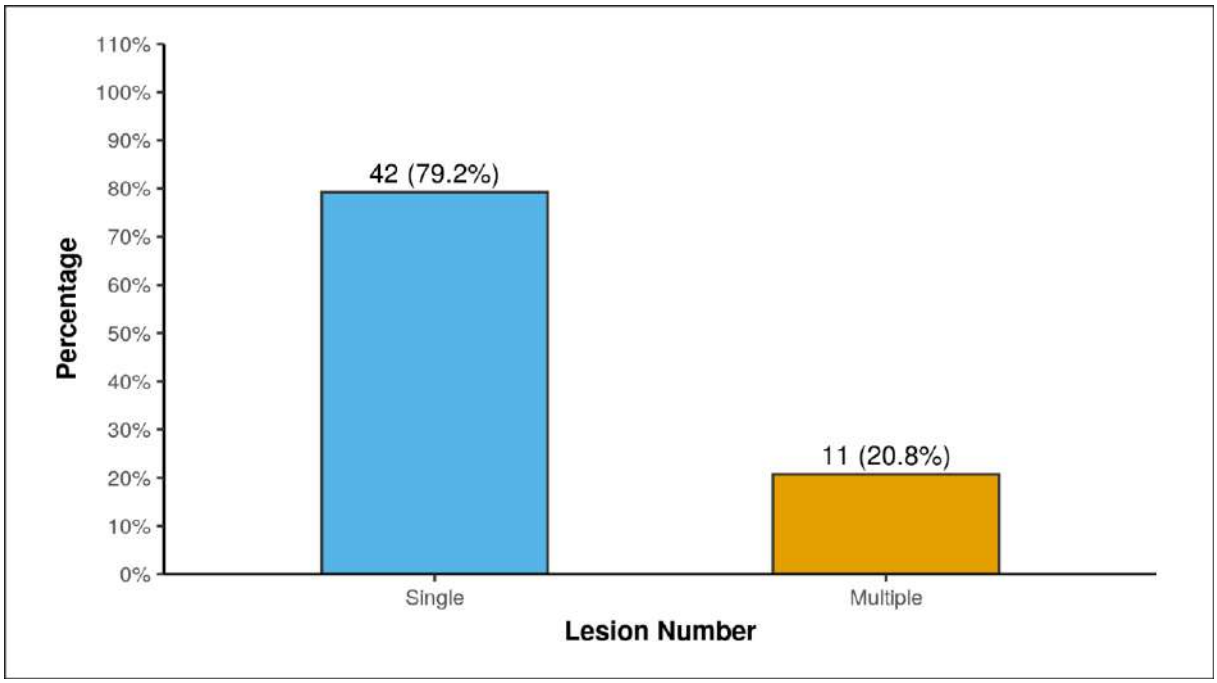


Figure 19: Distribution of lesion number

Distribution of the participants in terms of 'Number of Lesions'

Number Of Lesions	
Mean (SD)	1.38 (0.86)
Median (IQR)	1 (1-1)
Range	1 – 5

Table 13- Distribution of number of lesions

The mean (SD) number of lesions was 1.38 (0.86). The median number of lesions (IQR) was 1.00 (1-1). The number of lesions ranged from 1 to 5.

The skewness of the data was 2.42, suggesting that the data was positively skewed, thus suggesting it was not normally distributed. The kurtosis of the data was 5.59, indicating that the data was not normally distributed. Shapiro-Wilk test for the data was significant ($p = <0.001$), suggesting that the data was not normally distributed. There appeared to be only one mode/peak in the data, thus making it unimodal.

Since none of the three criteria (skewness, kurtosis, Shapiro-Wilk test) suggested normality, the data appeared not customarily distributed (it did not follow a bell-shaped curve).

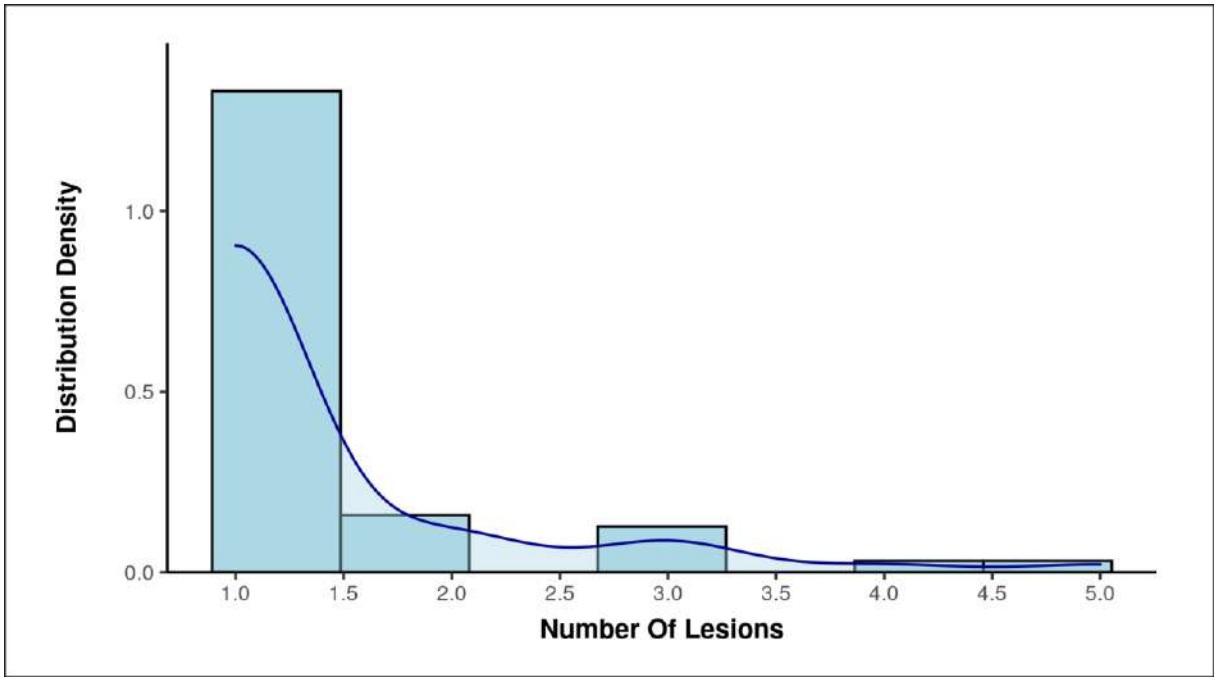


Figure 20: Distribution of number of lesions

The following histogram is plotted with the actual counts, and an ideal bell-shaped curve is superimposed on top for reference:

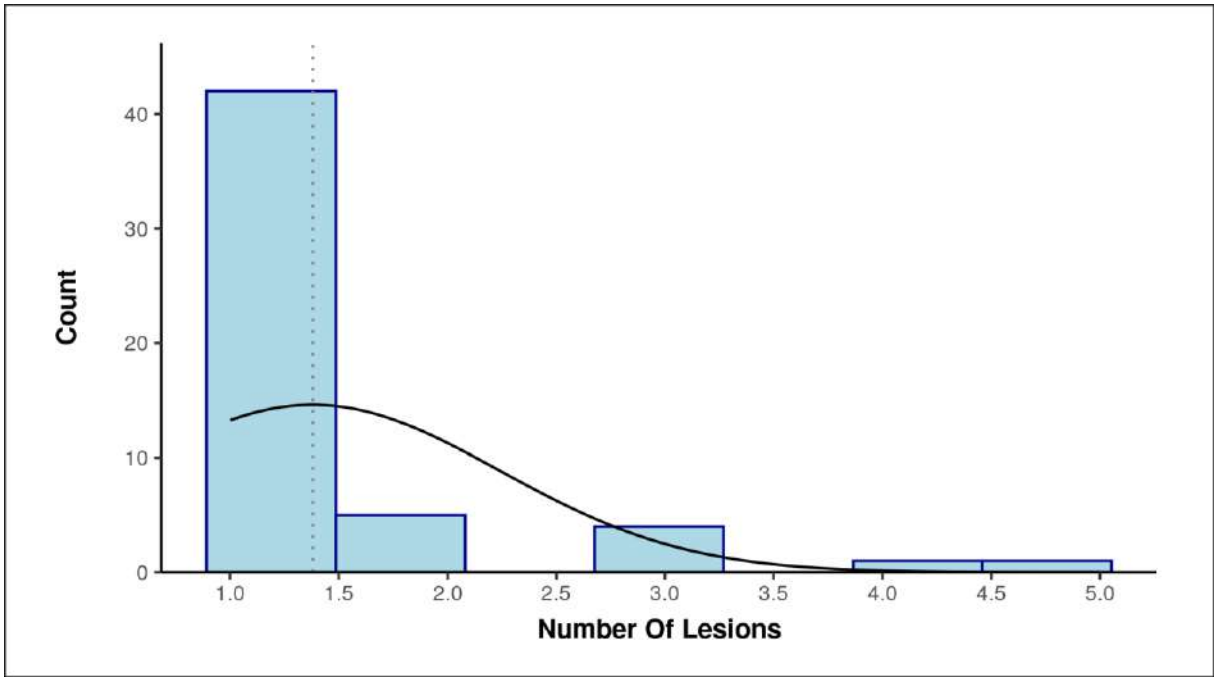


Figure 21: Distribution of number of lesions

Summary of All Parameters

All Parameters	Mean ± SD || Median (IQR) || Min-Max OR N (%)
Age (Years)	62.15 ± 12.52 || 61.00 (55.00-72.00) || 23.00 - 84.00
Gender	
Male	46 (86.8%)
Female	7 (13.2%)
VIRADS	
VIRADS 1	3 (5.7%)
VIRADS 2	8 (15.1%)
VIRADS 3	7 (13.2%)
VIRADS 4	16 (30.2%)
VIRADS 5	19 (35.8%)
VIRADS Category	
VIRADS 1-2	11 (20.8%)
VIRADS 3-5	42 (79.2%)
Largest dimensions (cm)	3.90 ± 2.33 || 3.30 (2.00-5.30) || 0.50 - 10.40
T Stage	
T0	1 (1.9%)
Ta	15 (28.3%)
T1	13 (24.5%)
T2	24 (45.3%)
Invasion	
Muscle Invasive	24 (45.3%)

All Parameters	Mean ± SD || Median (IQR) || Min-Max OR N (%)
Non-Muscle Invasive	29 (54.7%)
Grade	
Low	23 (44.2%)
High	29 (55.8%)
Hydronephrosis (Present)	13 (24.5%)
Hydronephrosis Laterality	
None	40 (75.5%)
Unilateral	6 (11.3%)
Bilateral	7 (13.2%)
Lesion Number	
Single	42 (79.2%)
Multiple	11 (20.8%)
Number Of Lesions	1.38 ± 0.86 || 1.00 (1.00-1.00) || 1.00 - 5.00

Table 14- Summary of parameters

The mean Age (Years) was 62.15 ± 12.52.

46 (86.8%) participants were Male, and 7 (13.2%) were Female.

3 (5.7%) of the participants had VIRADS 1. 8 (15.1%) of the participants had VIRADS 2. 7 (13.2%) of the participants had VIRADS 3. 16 (30.2%) of the participants had VIRADS 4. 19 (35.8%) of the participants had VIRADS 5.

11 (20.8%) of the participants had VIRADS Category 1-2. 42 (79.2%) of the participants had VIRADS Category 3-5.

The mean largest dimensions (cm) were 3.90 ± 2.33.

1 (1.9%) of the participants had T Stage: T0. 15 (28.3%) of the participants had T Stage: Ta. 13 (24.5%) of the participants had T Stage: T1. 24 (45.3%) of the participants had T Stage: T2.

24 (45.3%) of the participants had Muscle Invasion, and 29 (54.7%) had no muscle invasion.

23 (44.2%) of the participants had low-grade bladder cancer, and 29 (55.8%) had high-grade bladder cancer.

13 (24.5%) participants had Hydronephrosis, and 40 (75.5%) had no Hydronephrosis.

40 (75.5%) participants had no Hydronephrosis .6 (11.3%) participants had unilateral Hydronephrosis 7 (13.2%) of the participants had bilateral Hydronephrosis.

42 (79.2%) of the participants had single lesion, and 11 (20.8%) had multiple lesions.

The mean number Of Lesions was 1.38 ± 0.86.

Association between 'VIRADS' and 'T Stage'

T Stage	VIRADS						Fisher's Exact Test	
	VIRADS 1	VIRADS 2	VIRADS 3	VIRADS 4	VIRADS 5	Total	χ2	P Value
T0	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	57.948	<0.001
Ta	2 (66.7%)	6 (75.0%)	4 (57.1%)	3 (18.8%)	0 (0.0%)	15 (28.3%)		

T Stage	VIRADS						Fisher's Exact Test	
	VIRADS 1	VIRADS 2	VIRADS 3	VIRADS 4	VIRADS 5	Total	$\chi 2$	P Value
T1	0 (0.0%)	2 (25.0%)	3 (42.9%)	7 (43.8%)	1 (5.3%)	13 (24.5%)		
T2	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (37.5%)	18 (94.7%)	24 (45.3%)		
Total	3 (100.0%)	8 (100.0%)	7 (100.0%)	16 (100.0%)	19 (100.0%)	53 (100.0%)		

T Stage	Adjusted P Values
T0 vs. Ta	0.375
T0 vs. T1	0.176
T0 vs. T2	0.080
Ta vs. T1	0.176
Ta vs. T2	<0.001
T1 vs. T2	<0.001

VIRADS	Adjusted- P Values
VIRADS 1 vs. VIRADS 2	0.357
VIRADS 1 vs. VIRADS 3	0.198
VIRADS 1 vs. VIRADS 4	0.041
VIRADS 1 vs. VIRADS 5	0.003
VIRADS 2 vs. VIRADS 3	0.608
VIRADS 2 vs. VIRADS 4	0.053
VIRADS 2 vs. VIRADS 5	<0.001
VIRADS 3 vs. VIRADS 4	0.144
VIRADS 3 vs. VIRADS 5	<0.001
VIRADS 4 vs. VIRADS 5	0.003

Table 15-Association between 'VIRADS' and 'T Stage'

Fisher's exact test was used to explore the association between 'VIRADS' and 'T Stage' as more than 20% of the total number of cells had an expected count of less than 5.

There was a significant difference between the various groups in terms of the distribution of T Stage ($\chi 2 = 57.948$, p = <0.001).

Strength of association between the two variables (Cramer's V) = 0.6 (High Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.55 (High Association)

33.3% of the participants in the group [VIRADS 1] had [T Stage: T0]. 66.7% of the participants in the group [VIRADS 1] had [T Stage: Ta]. 0.0% of the participants in the group [VIRADS 1]

had [T Stage: T1]. 0.0% of the participants in the group [VIRADS 1] had [T Stage: T2]. 0.0% of the participants in the group [VIRADS 2] had [T Stage: T0]. 75.0% of the participants in the group [VIRADS 2] had [T Stage: Ta]. 25.0% of the participants in the group [VIRADS 2] had [T Stage: T1]. 0.0% of the participants in the group [VIRADS 2] had [T Stage: T2]. 0.0% of the participants in the group [VIRADS 3] had [T Stage: T0]. 57.1% of the participants in the group [VIRADS 3] had [T Stage: Ta]. 42.9% of the participants in the group [VIRADS 3] had [T Stage: T1]. 0.0% of the participants in the group [VIRADS 3] had [T Stage: T2]. 0.0% of the participants in the group [VIRADS 4] had [T Stage: T0]. 18.8% of the participants in the group [VIRADS 4] had [T Stage: Ta]. 43.8% of the participants in the group [VIRADS 4] had [T Stage: T1]. 37.5% of the participants in the group [VIRADS 4] had [T Stage: T2]. 0.0% of the participants in the group [VIRADS 5] had [T Stage: T0]. 0.0% of the participants in the group [VIRADS 5] had [T Stage: Ta]. 5.3% of the participants in the group [VIRADS 5] had [T Stage: T1]. 94.7% of the participants in the group [VIRADS 5] had [T Stage: T2].

Participants in the group VIRADS: VIRADS 1 had the largest proportion of T Stage: T0. Participants in the group VIRADS 2 had the largest proportion of T Stage: Ta. Participants in the group VIRADS 4 had the largest proportion of T Stage: T1. Participants in the group VIRADS 5 had the largest proportion of T Stage: T2.

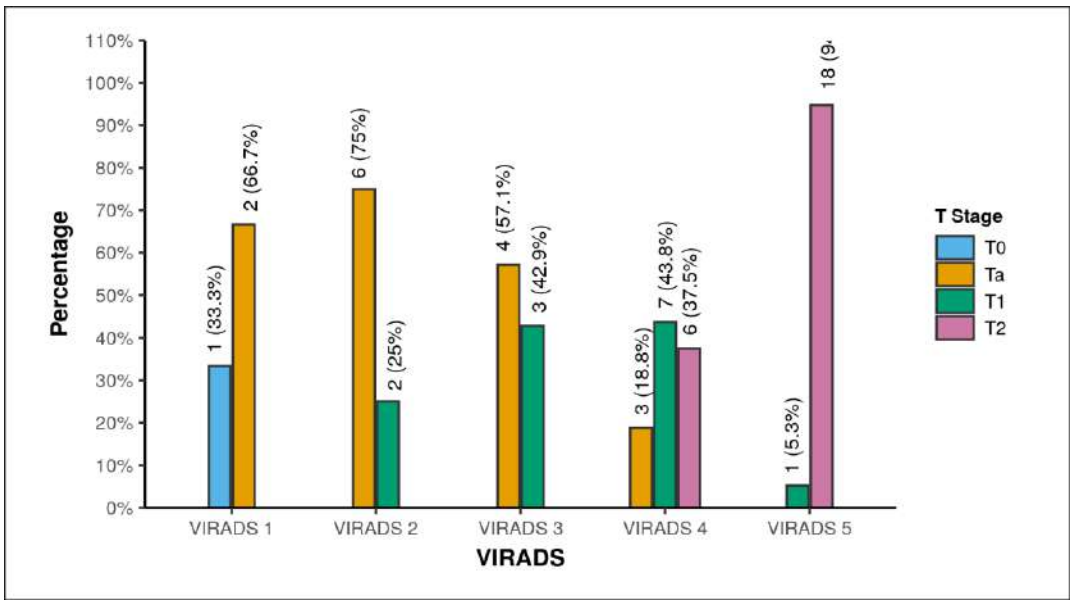


Figure 22: Association between VIRADS and T Stage

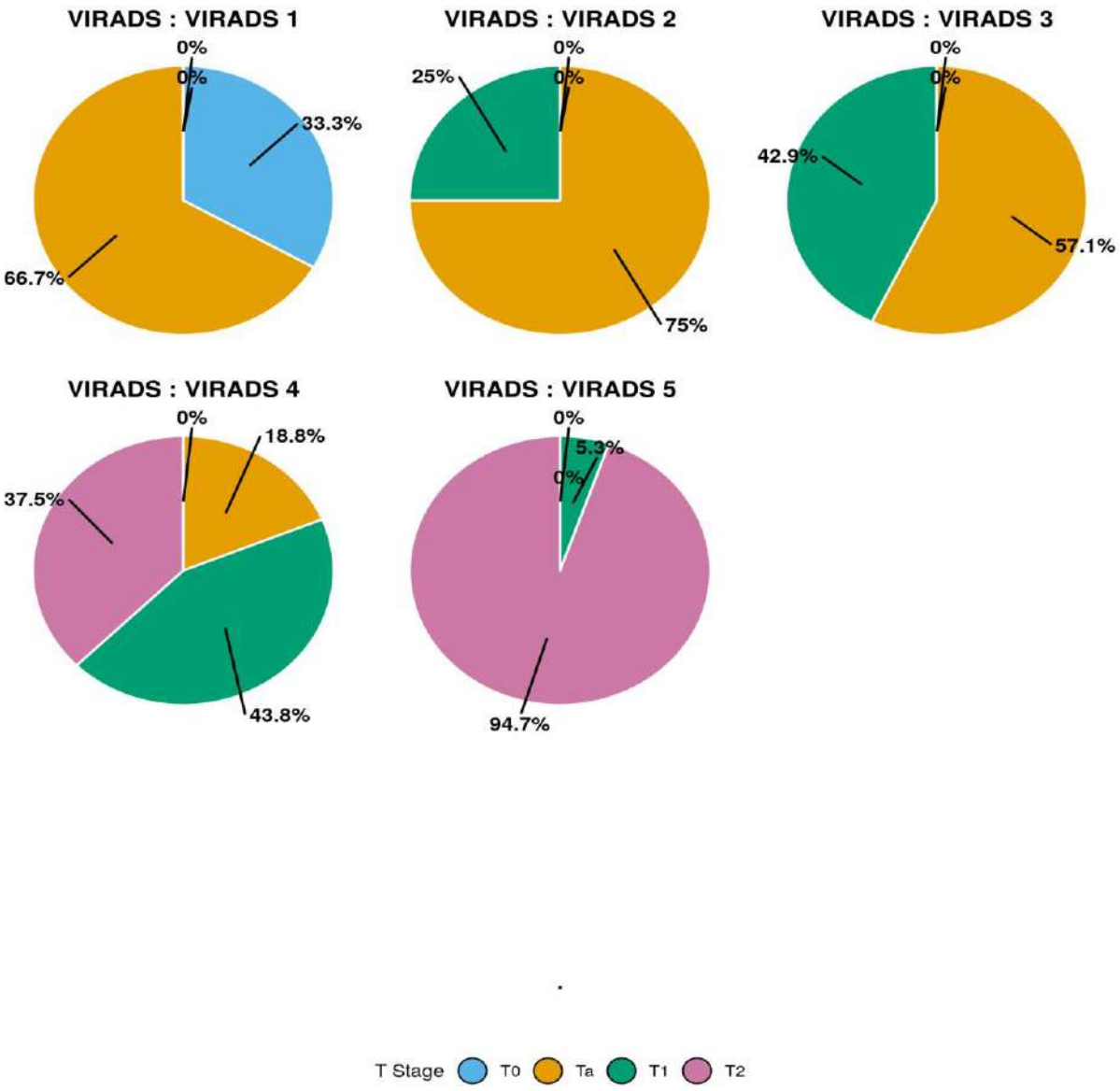


Figure 23: Association between VIRADS and T Stage

Association between 'VIRADS' and 'Invasion'

Invasion	VIRADS						Fisher's Exact Test	
	VIRADS 1	VIRADS 2	VIRADS 3	VIRADS 4	VIRADS 5	Total	χ2	P Value
Muscle Invasive	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (37.5%)	18 (94.7%)	24 (45.3%)	34.042	<0.001
Non-Muscle Invasive	3 (100.0%)	8 (100.0%)	7 (100.0%)	10 (62.5%)	1 (5.3%)	29 (54.7%)		
Total	3 (100.0%)	8 (100.0%)	7 (100.0%)	16 (100.0%)	19 (100.0%)	53 (100.0%)		

VIRADS	Adjusted P Values
VIRADS 1 vs. VIRADS 2	1.000
VIRADS 1 vs. VIRADS 3	1.000
VIRADS 1 vs. VIRADS 4	0.739
VIRADS 1 vs. VIRADS 5	0.006
VIRADS 2 vs. VIRADS 3	1.000
VIRADS 2 vs. VIRADS 4	0.133
VIRADS 2 vs. VIRADS 5	<0.001

VIRADS	Adjusted P Values
VIRADS 3 vs. VIRADS 4	0.207
VIRADS 3 vs. VIRADS 5	<0.001
VIRADS 4 vs. VIRADS 5	0.002

Table 16-Association between 'VIRADS' and 'Invasion'

Fisher's exact test was used to explore the association between 'VIRADS' and 'Invasion' as more than 20% of the total number of cells had an expected count of less than 5.

There was a significant difference between the various groups in terms of the distribution of invasion ($\chi 2 = 34.042$, $p = <0.001$).

Strength of association between the two variables (Cramer's V) = 0.8 (High Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.76 (High Association)

0.0% of the participants in the group [VIRADS 1] had [Invasion: Muscle Invasive]. 100.0% of the participants in the group [VIRADS 1] had [Invasion: Non-Muscle Invasive]. 0.0% of the participants in the group [VIRADS 2] had [Invasion: Muscle Invasive]. 100.0% of the participants in the group [VIRADS 2] had [Invasion: Non-Muscle Invasive]. 0.0% of the participants in the group [VIRADS 3] had [Invasion: Muscle Invasive]. 100.0% of the participants in the group [VIRADS 3] had [Invasion: Non-Muscle Invasive]. 37.5% of the participants in the group [VIRADS 4] had [Invasion: Muscle Invasive]. 62.5% of the participants in the group [VIRADS 4] had [Invasion: Non-Muscle Invasive]. 94.7% of the participants in the group [VIRADS 5] had [Invasion: Muscle Invasive]. 5.3% of the participants in the group [VIRADS 5] had [Invasion: Non-Muscle Invasive].

Participants in the group VIRADS 5 had the largest proportion of muscle invasive bladder cancer. Participants in the group VIRADS: VIRADS 1, VIRADS 2, VIRADS 3 had the largest proportion of Non-Muscle Invasive bladder cancer.

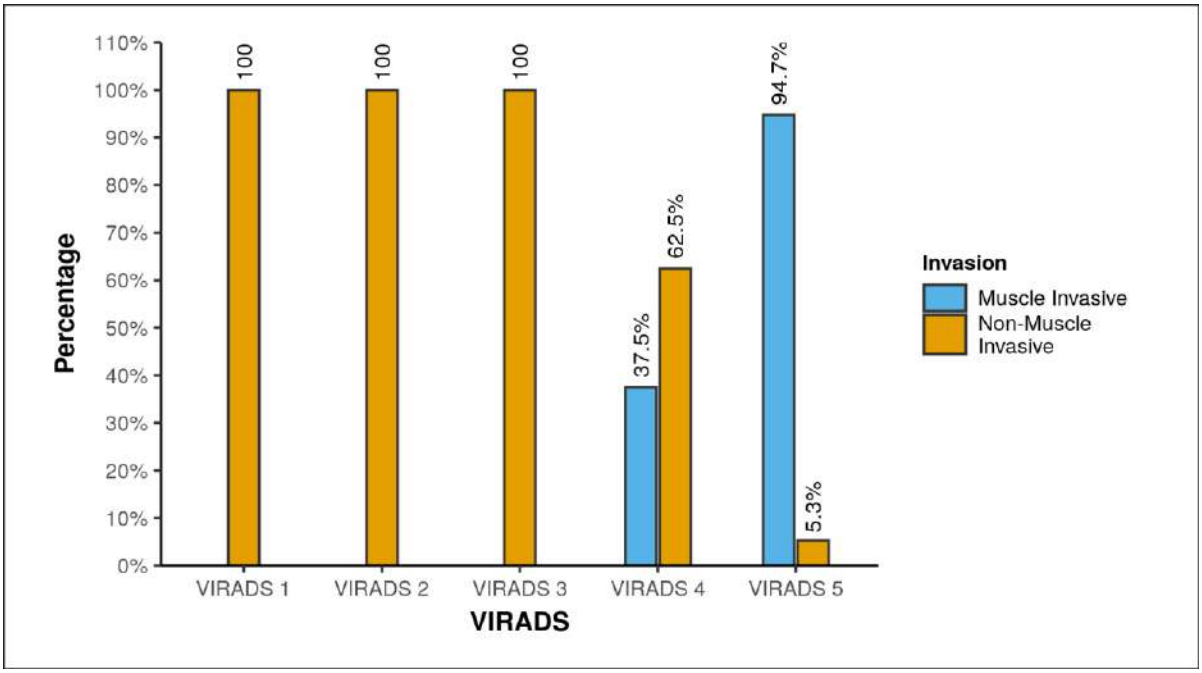


Figure 24: Association between VIRADS and Invasion

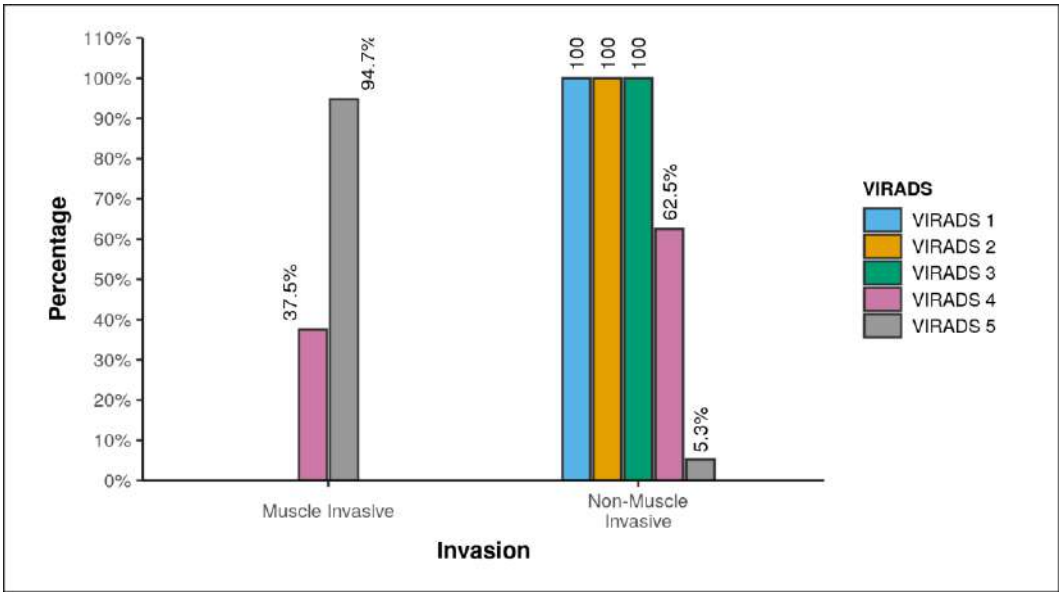


Figure 25: Association between VIRADS and Invasion

Association between 'VIRADS' and 'Grade'

Grade	VIRADS						Fisher's Exact Test	
	VIRADS 1	VIRADS 2	VIRADS 3	VIRADS 4	VIRADS 5	Total	χ2	P Value
Low	1 (50.0 %)	7 (87.5 %)	7 (100.0 %)	7 (43.8 %)	1 (5.3%)	23 (44.2 %)	26.623	<0.001
High	1 (50.0 %)	1 (12.5 %)	0 (0.0%)	9 (56.2 %)	18 (94.7 %)	29 (55.8 %)		
Total	2 (100.0 %)	8 (100.0 %)	7 (100.0 %)	16 (100.0 %)	19 (100.0 %)	52 (100.0 %)		

VIRADS	Adjusted P Values
VIRADS 1 vs. VIRADS 2	0.472
VIRADS 1 vs. VIRADS 3	0.318
VIRADS 1 vs. VIRADS 4	1.000
VIRADS 1 vs. VIRADS 5	0.310

VIRADS	Adjusted P Values
VIRADS 2 vs. VIRADS 3	1.000
VIRADS 2 vs. VIRADS 4	0.158
VIRADS 2 vs. VIRADS 5	<0.001
VIRADS 3 vs. VIRADS 4	0.047
VIRADS 3 vs. VIRADS 5	<0.001
VIRADS 4 vs. VIRADS 5	0.043

Table 17-Association between 'VIRADS' and 'Grade'

Fisher's exact test was used to explore the association between 'VIRADS' and 'Grade' as more than 20% of the total number of cells had an expected count of less than 5.

There was a significant difference between the various groups in terms of distribution of Grade ($\chi 2 = 26.623$, p = <0.001).

Strength of association between the two variables (Cramer's V) = 0.72 (High Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.66 (High Association)

50.0% of the participants in the group [VIRADS 1] had [Grade: Low]. 50.0% of the participants in the group [VIRADS 1] had [Grade: High]. 87.5% of the participants in the group [VIRADS 2] had [Grade: Low]. 12.5% of the participants in the group [VIRADS 2] had [Grade: High]. 100.0% of the participants in the group [VIRADS 3] had [Grade: Low]. 0.0% of the participants in the group [VIRADS: VIRADS 3] had [Grade: High]. 43.8% of the participants in the group [VIRADS 4] had [Grade: Low]. 56.2% of the participants in the group [VIRADS 4] had [Grade: High]. 5.3% of the participants in the group [VIRADS 5] had [Grade: Low]. 94.7% of the participants in the group [VIRADS 5] had [Grade: High].

Participants in the group VIRADS 3 had the largest proportion of low grade cancer. Participants in the group VIRADS 5 had the largest proportion of high grade cancer.

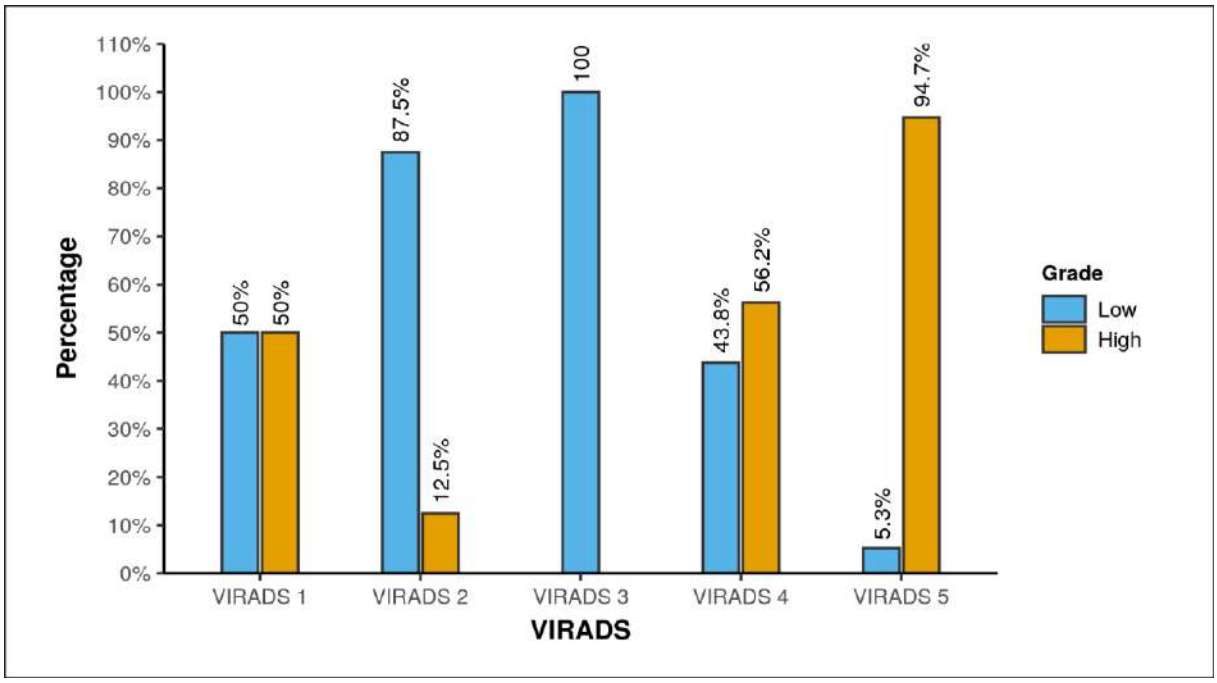


Figure 26: Association between VIRADS and Grade

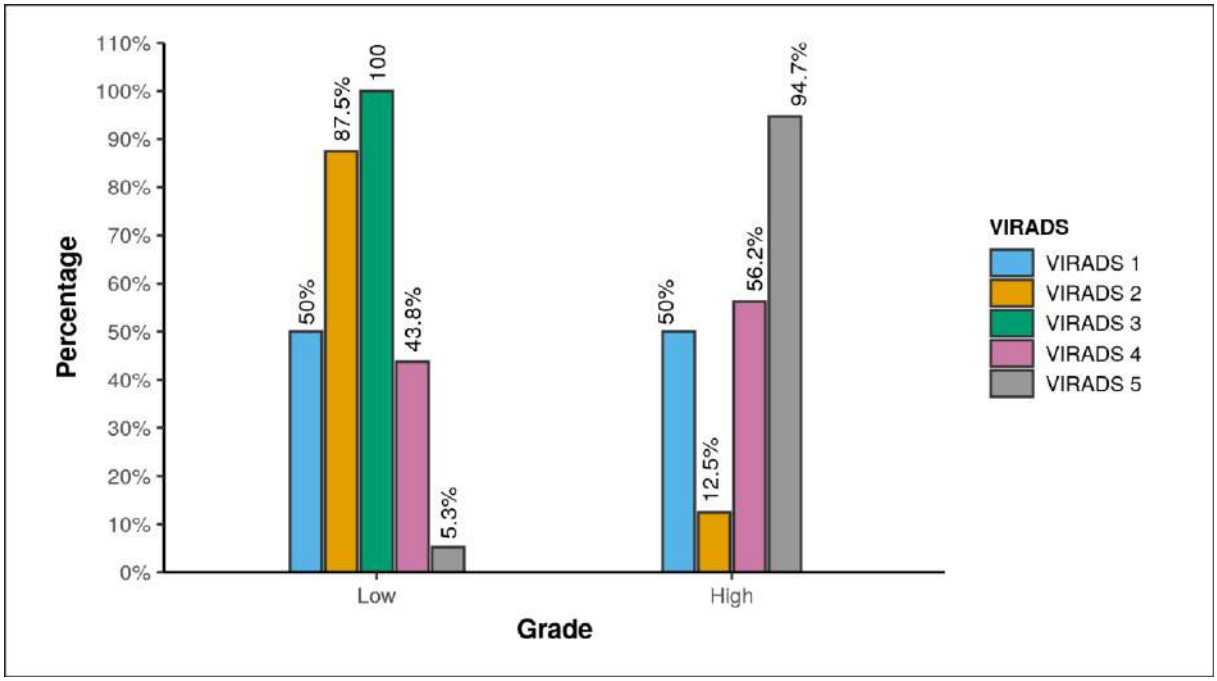


Figure 27: Association between VIRADS and Grade

Association between 'T Stage' and 'Largest dimensions (cm)'

Largest dimensions (cm)	T Stage				Kruskal Wallis Test	
	T0	Ta	T1	T2	χ2	p-value
Mean (SD)	0.50 (NA)	2.20 (1.47)	4.27 (1.64)	4.91 (2.46)	17.437	0.001
Median (IQR)	0.5 (0.5-0.5)	1.9 (1.1-2.45)	4.4 (3-5)	4.8 (3-6)		
Min - Max	0.5 - 0.5	0.6 - 5.3	1.5 - 7.3	1.4 - 10.4		

Pairwise Comparison of Subcategories of T Stage	Adjusted P Value
T0 - T1	0.307
T0 - T2	0.214
T1 - T2	0.999
T0 – Ta	0.947
T1 – Ta	0.029
T2 – Ta	0.001

Table 18-Association between T Stage and largest dimensions

The variable's largest dimensions (cm) were not generally distributed in the four subgroups of the variable T Stage. Thus, non-parametric (Kruskal Wallis) tests were used for group comparisons.

The mean (SD) of the largest dimensions (cm) in the T Stage: T0 group was 0.50 (NA). The mean (SD) of the largest dimensions (cm) in the T Stage: Ta group was 2.20 (1.47). The mean (SD) of the largest dimensions (cm) in the T Stage: T1 group was 4.27 (1.64). The mean (SD) of the largest dimensions (cm) in the T Stage: T2 group was 4.91 (2.46). The median (IQR) of the largest dimensions (cm) in the T Stage: T0 group was 0.5 (0.5-0.5). The median (IQR) of the largest dimensions (cm) in the T Stage: Ta group was 1.9 (1.1-2.45). The median (IQR) of the largest dimensions (cm) in the T Stage: T1 group was 4.4 (3-5). The median (IQR) of the largest dimensions (cm) in the T Stage: T2 group was 4.8 (3-6). The Largest dimensions (cm) in the T Stage: T0 ranged from 0.5 - 0.5. The Largest dimensions (cm) in the T Stage, Ta, ranged from 0.6 - 5.3. The Largest dimensions (cm) in the T Stage: T1 ranged from 1.5 - 7.3. The Largest dimensions (cm) in the T Stage: T2 ranged from 1.4 - 10.4.

There was a significant difference between the four groups in terms of largest dimensions (cm) ($\chi 2 = 17.437$, $p = 0.001$), with the median largest dimensions (cm) being highest in the T Stage: T2 group.

Strength of Association (Kendall's Tau) = 0.42 (Medium Effect Size)

The bar graph below depicts the means of the largest dimensions (cm) in the four groups.

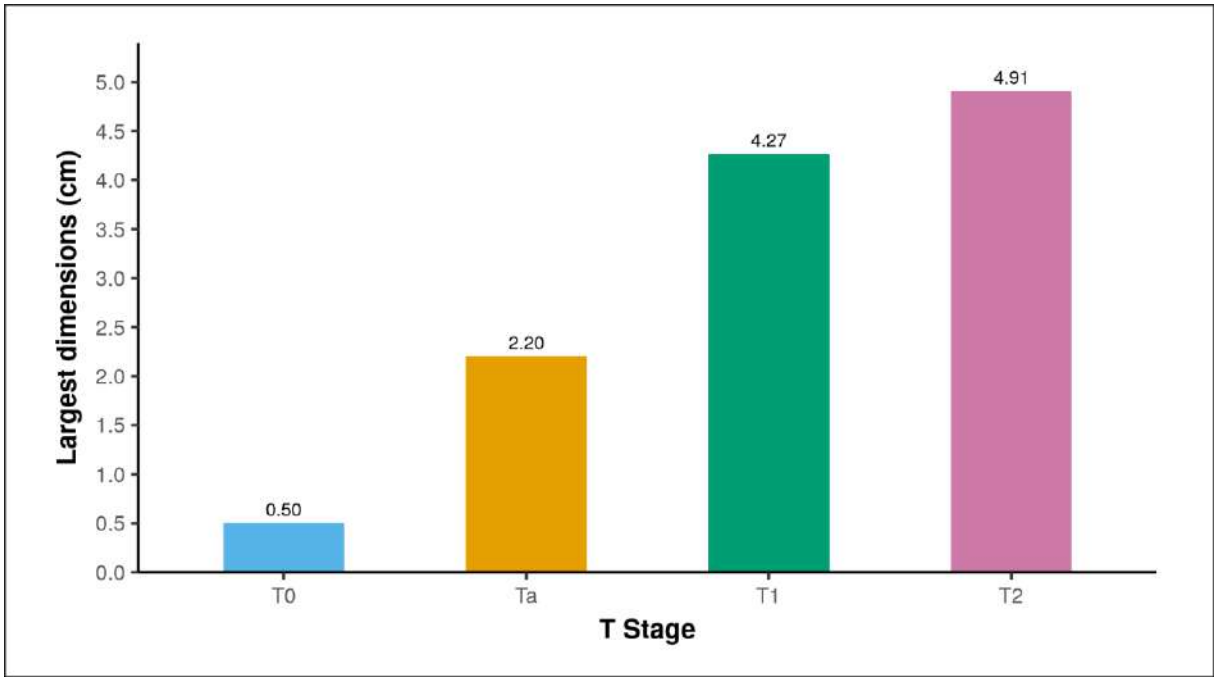


Figure 28: Association Between T Stage and largest dimensions (cm)

Association between 'T Stage' and 'Grade'

Grade	T Stage				Chi-Squared Test	
	Ta	T1	lT2	Total	χ2	P Value
Low	14 (93.3%)	8 (61.5%)	1 (4.2%)	23 (44.2%)	31.857	<0.001
High	1 (6.7%)	5 (38.5%)	23 (95.8%)	29 (55.8%)		
Total	15 (100.0%)	13 (100.0%)	24 (100.0%)	52 (100.0%)		

T Stage	Adjusted P Values
Ta vs. T1	0.069
Ta vs. T2	<0.001
T1 vs. T2	<0.001

Table 19-Association between T Stage and Grade

A chi-squared test explored the association between 'T Stage' and 'Grade.'

There was a significant difference between the various groups regarding the Grade distribution ($\chi 2 = 31.857$, $p = <0.001$).

Strength of association between the two variables (Cramer's V) = 0.78 (High Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.76 (High Association)

93.3% of the participants in the group [T Stage: Ta] had [Grade: Low]. 6.7% of the participants in the group [T Stage: Ta] had [Grade: High]. 61.5% of the participants in the group [T Stage: T1] had [Grade: Low]. 38.5% of the participants in the group [T Stage: T1] had [Grade: High]. 4.2% of the participants in the group [T Stage: T2] had [Grade: Low]. 95.8% of the participants in the group [T Stage: T2] had [Grade: High].

Participants in the group T Stage: Ta had the largest proportion of low grade bladder cancer, and participants in the group T Stage: T2 had the largest proportion of participants with high grade bladder cancer

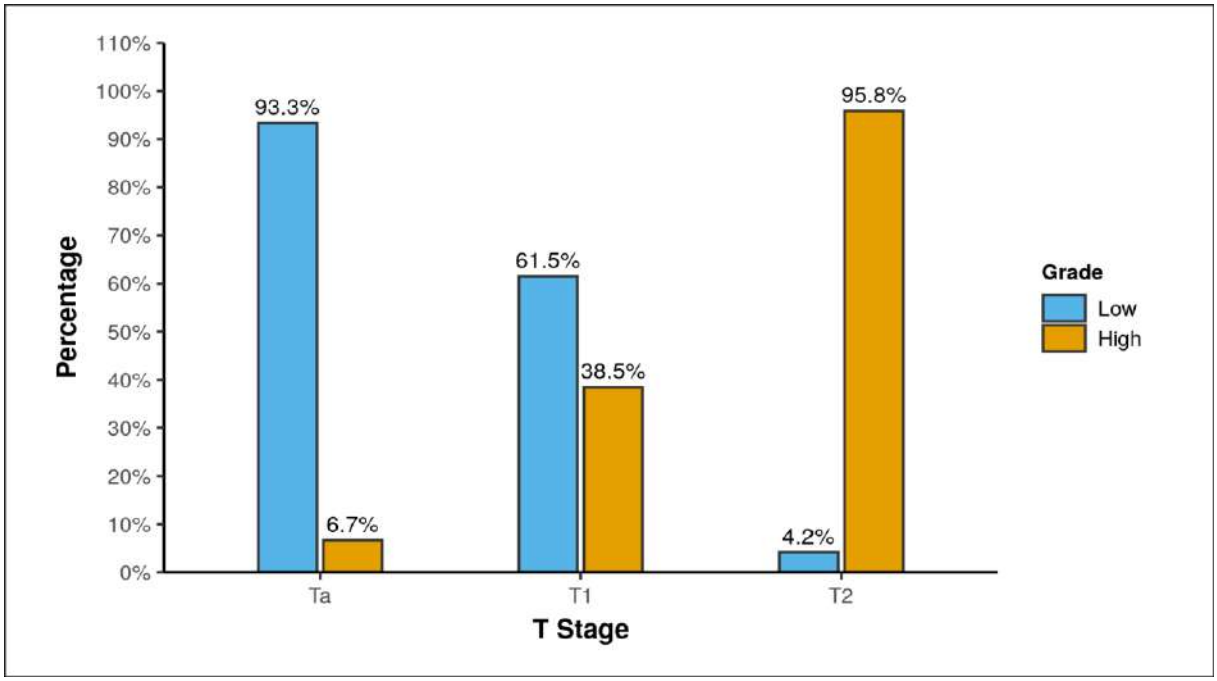


Figure 29: Association between T Stage and Grade

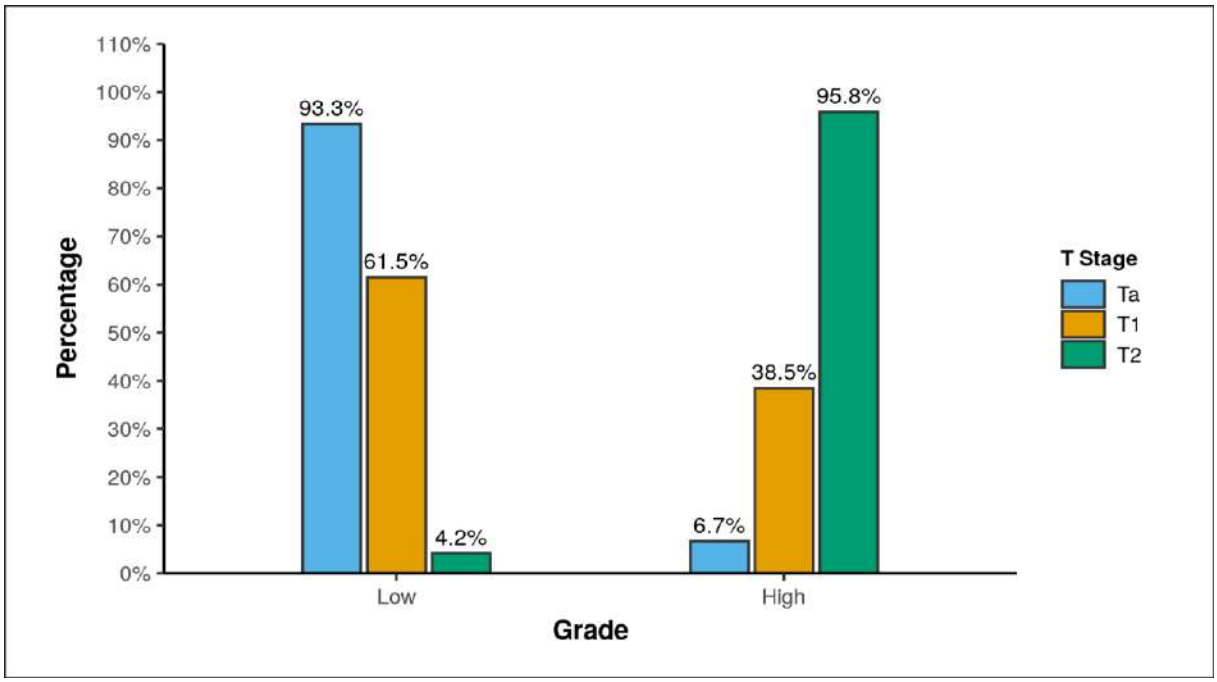


Figure 30: Association between T Stage and Grade

Association between 'T Stage' and ' Hydronephrosis'

Hydronephrosis	T Stage					Fisher's Exact Test	
	T0	Ta	T1	T2	Total	χ2	P Value
Present	0 (0.0%)	0 (0.0%)	2 (15.4%)	11 (45.8%)	13 (24.5%)	11.672	0.003
Absent	1 (100.0%)	15 (100.0%)	11 (84.6%)	13 (54.2%)	40 (75.5%)		
Total	1 (100.0%)	15 (100.0%)	13 (100.0%)	24 (100.0%)	53 (100.0%)		

T Stage	Adjusted P Values
T0 vs. Ta	1.000
T0 vs. T1	1.000
T0 vs. T2	1.000
Ta vs. T1	0.413
Ta vs. T2	0.014
T1 vs. T2	0.249

Table 20- Association between T Stage and Hydronephrosis

Fisher's exact test was used to explore the association between 'T Stage' and 'Hydronephrosis' as more than 20% of the total cells had an expected count of less than 5.

The distribution of any Hydronephrosis varied significantly between the various groups ($\chi 2$ = 11.672, p = 0.003).

Strength of association between the two variables (Cramer's V) = 0.47 (Moderate Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.41 (Moderate Association)

0.0% of the participants in the group [T Stage: T0] had [Hydronephrosis: Present]. 100.0% of the participants in the group [T Stage: T0] had [Hydronephrosis: Absent]. 0.0% of the participants in the group [T Stage: Ta] had [Hydronephrosis: Present]. 100.0% of the participants in the group [T Stage: Ta] had [Hydronephrosis: Absent]. 15.4% of the participants in the group [T Stage: T1] had [Hydronephrosis: Present]. 84.6% of the participants in the group [T Stage: T1] had [Hydronephrosis: Absent]. 45.8% of the participants in the group [T Stage: T2] had [Hydronephrosis: Present]. 54.2% of the participants in the group [T Stage: T2] had [Hydronephrosis: Absent].

Group T Stage: T2 participants had the most significant proportion of patients with Hydronephrosis. Participants in the group T Stage: T0, Ta had the most significant proportion of participants with no Hydronephrosis.

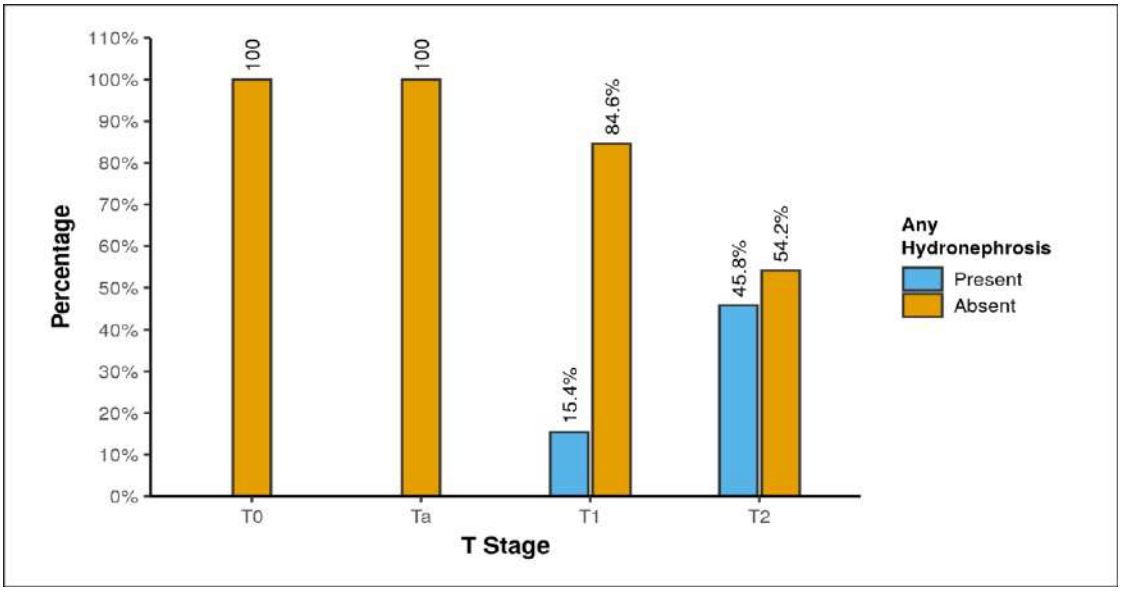


Figure 31: Association between T Stage and Hydronephrosis

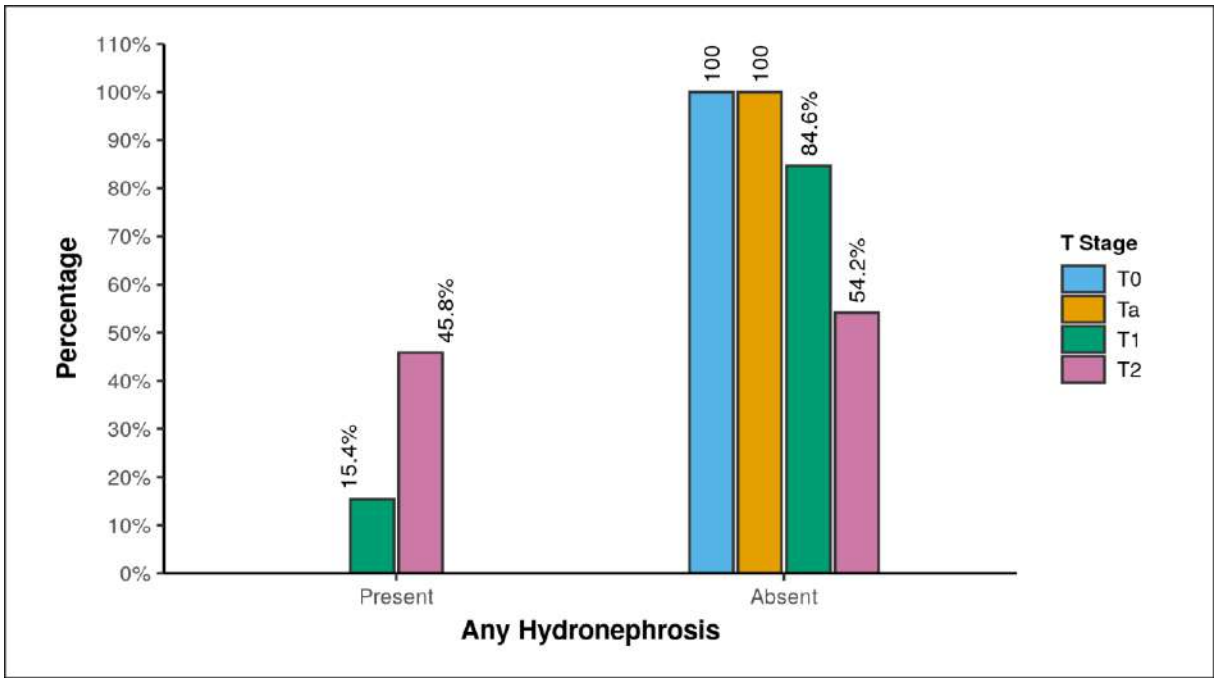


Figure 32: Association between T Stage and Hydronephrosis

Association between 'Invasion' and 'Grade'

Grade	Invasion			Chi-Squared Test	
	Muscle Invasive	Non-Muscle Invasive	Total	χ2	P Value
Low	1 (4.2%)	22 (78.6%)	23 (44.2%)	29.003	<0.001
High	23 (95.8%)	6 (21.4%)	29 (55.8%)		
Total	24 (100.0%)	28 (100.0%)	52 (100.0%)		

Table 21-Association between Invasion and Grade

A chi-squared test explored the association between 'Invasion' and 'Grade.'

There was a significant difference between the various groups regarding the Grade distribution ($\chi2 = 29.003$, $p = <0.001$).

Strength of association between the two variables (Cramer's V) = 0.75 (High Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.74 (High Association)

4.2% of the participants in the group [Invasion: Muscle Invasive] had [Grade: Low]. 95.8% of the participants in the group [Invasion: Muscle Invasive] had [Grade: High]. 78.6% of the participants in the group [Invasion: Non-Muscle Invasive] had [Grade: Low]. 21.4% of the participants in the group [Invasion: Non-Muscle Invasive] had [Grade: High].

The Non-Muscle invasive participants had a more significant proportion of low-grade bladder cancer. Participants with muscle invasion had a more substantial proportion of high-grade bladder cancer.

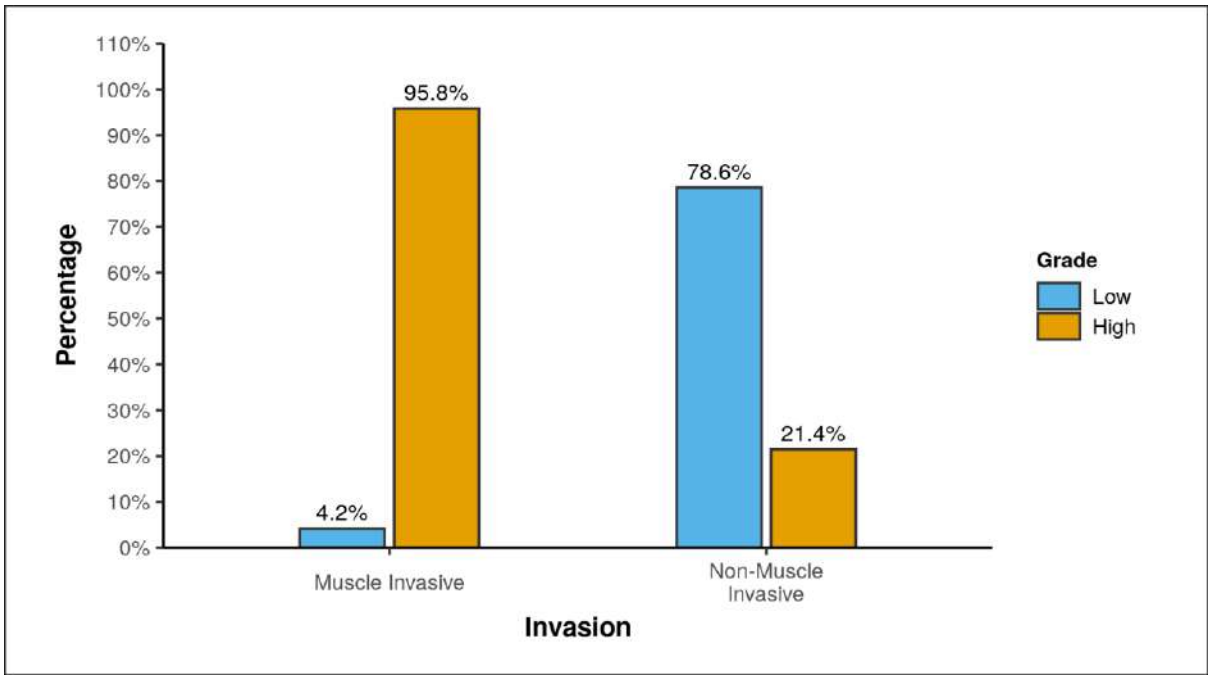


Figure 33: Association between Invasion and Grade

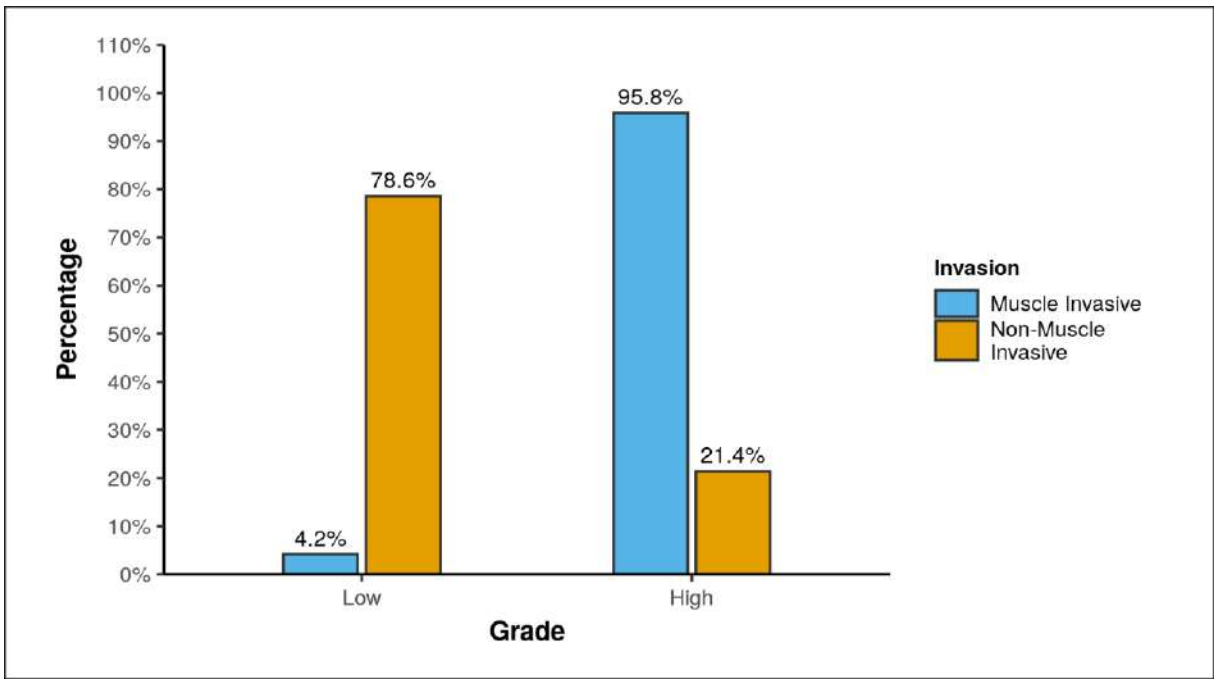


Figure 34: Association between Invasion and Grade

Association between 'Invasion' and ' Hydronephrosis'

Any Hydronephrosis	Invasion			Chi-Squared Test	
	Muscle Invasive	Non-Muscle Invasive	Total	χ2	P Value
Present	11 (45.8%)	2 (6.9%)	13 (24.5%)	10.755	0.001
Absent	13 (54.2%)	27 (93.1%)	40 (75.5%)		
Total	24 (100.0%)	29 (100.0%)	53 (100.0%)		

Table 22-Association between Invasion and Hydronephrosis

The chi-squared test explored the association between 'Invasion' and 'Hydronephrosis.'

The distribution of Hydronephrosis varied significantly between the various groups ($\chi 2 = 10.755$, $p = 0.001$).

Strength of association between the two variables (Cramer's V) = 0.45 (Moderate Association)
Strength of association between the two variables (Bias Corrected Cramer's V) = 0.43 (Moderate Association)

45.8% of the participants in the group [Invasion: Muscle Invasive] had [Hydronephrosis: Present]. 54.2% of the participants in the group [Invasion: Muscle Invasive] had [Hydronephrosis: Absent]. 6.9% of the participants in the group [Invasion: Non-Muscle Invasive] had [Hydronephrosis: Present]. 93.1% of the participants in the group [Invasion: Non-Muscle Invasive] had [Hydronephrosis: Absent].

The group with muscle invasion had the highest proportion of participants with Hydronephrosis, while the group with non-muscle invasion had a higher proportion of participants with absent Hydronephrosis.

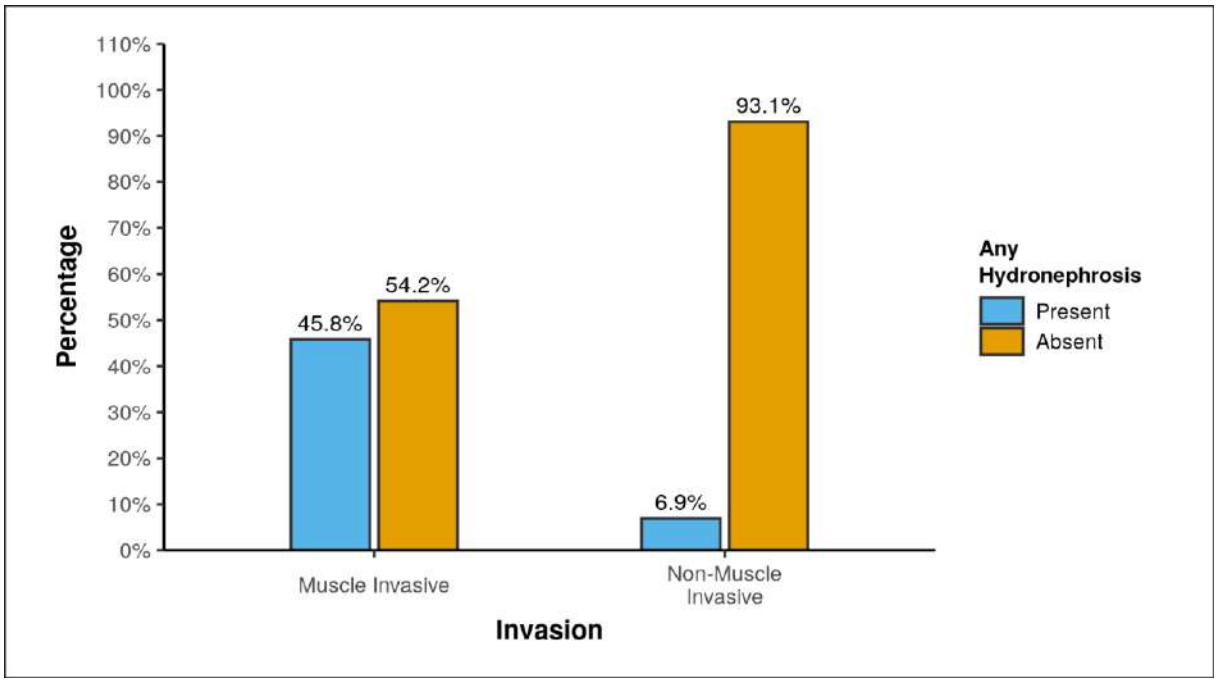


Figure 35: Association between Invasion and Hydronephrosis

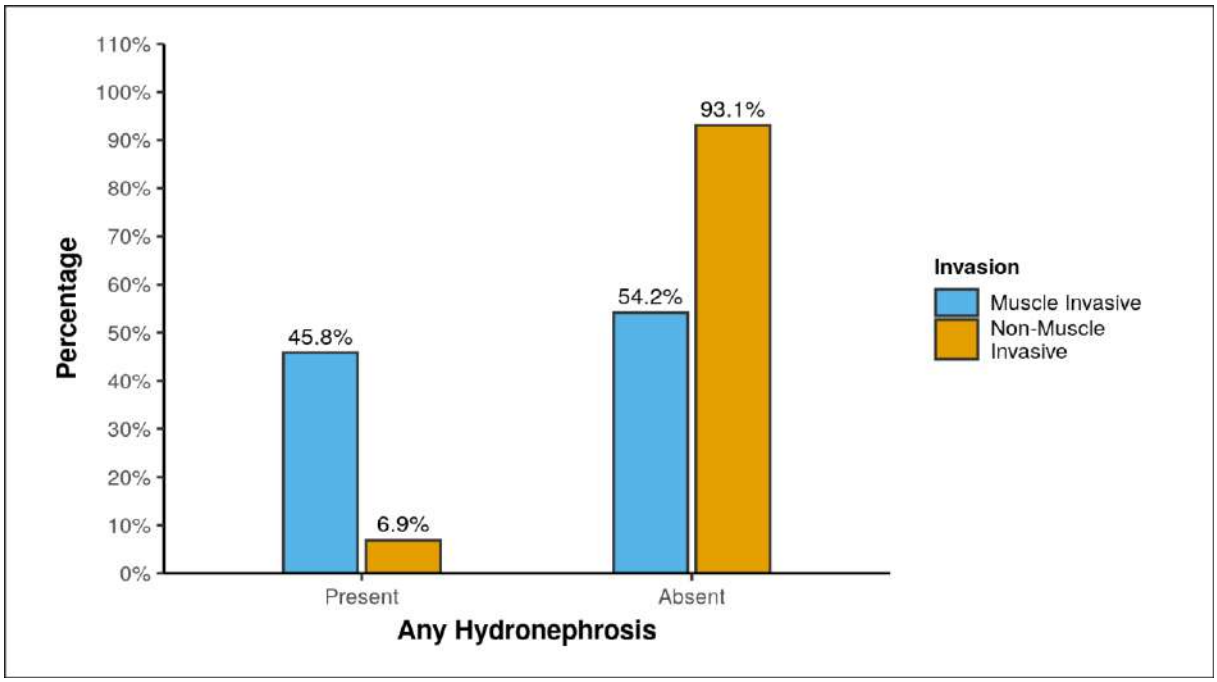


Figure 36: Association between Invasion and Hydronephrosis

Performance of Study Parameters for Predicting Invasion: Muscle Invasive vs. Non-Muscle Invasive

Description of Variables

Variable	Category(s) Suggesting Outcome Present	Category(s) Suggesting Outcome Absent	Total Positives	True Positives	True Negatives	False Positives	False Negatives
Invasion	Muscle Invasive	Non-Muscle Invasive	24 (45.3%)	-	-	-	-
VIRADS 2.3.4.5	VIRADS 2, VIRADS 3, VIRADS 4, VIRADS 5	VIRADS 1	50 (94.3%)	24 (45.3%)	3 (5.7%)	26 (49.1%)	0 (0.0%)
VIRADS 3,4,5	VIRADS 3, VIRADS 4, VIRADS 5	VIRADS 1, VIRADS 2	42 (79.2%)	24 (45.3%)	11 (20.8%)	18 (34.0%)	0 (0.0%)
VIRADS 4,5	VIRADS 4, VIRADS 5	VIRADS 1, VIRADS 2, VIRADS 3	35 (66.0%)	24 (45.3%)	18 (34.0%)	11 (20.8%)	0 (0.0%)
VIRADS 5	VIRADS 5	VIRADS 1, VIRADS 2, VIRADS 3, VIRADS 4	19 (35.8%)	18 (34.0%)	28 (52.8%)	1 (1.9%)	6 (11.3%)

Primary Diagnostic Parameters

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
VIRADS 2,3,4,5	100.0% (86-100)	10.3% (2-27)	48.0% (34-63)	100.0% (29-100)	50.9% (37-65)
VIRADS 3,4,5	100.0% (86-100)	37.9% (21-58)	57.1% (41-72)	100.0% (72-100)	66.0% (52-78)
VIRADS 4,5	100.0% (86-100)	62.1% (42-79)	68.6% (51-83)	100.0% (81-100)	79.2% (66-89)
VIRADS 5	75.0% (53-90)	96.6% (82-100)	94.7% (74-100)	82.4% (65-93)	86.8% (75-95)

Table 23-Performance of study parameters

The pooled area under the curve (AUC) of VI-RADS score ≥3 predicting the MIBC status was 69%.

The pooled area under the curve (AUC) of VI-RADS score ≥4 predicting the MIBC status was 78%.

The pooled area under the curve (AUC) of VI-RADS score ≥5 predicting the MIBC status was 81%.

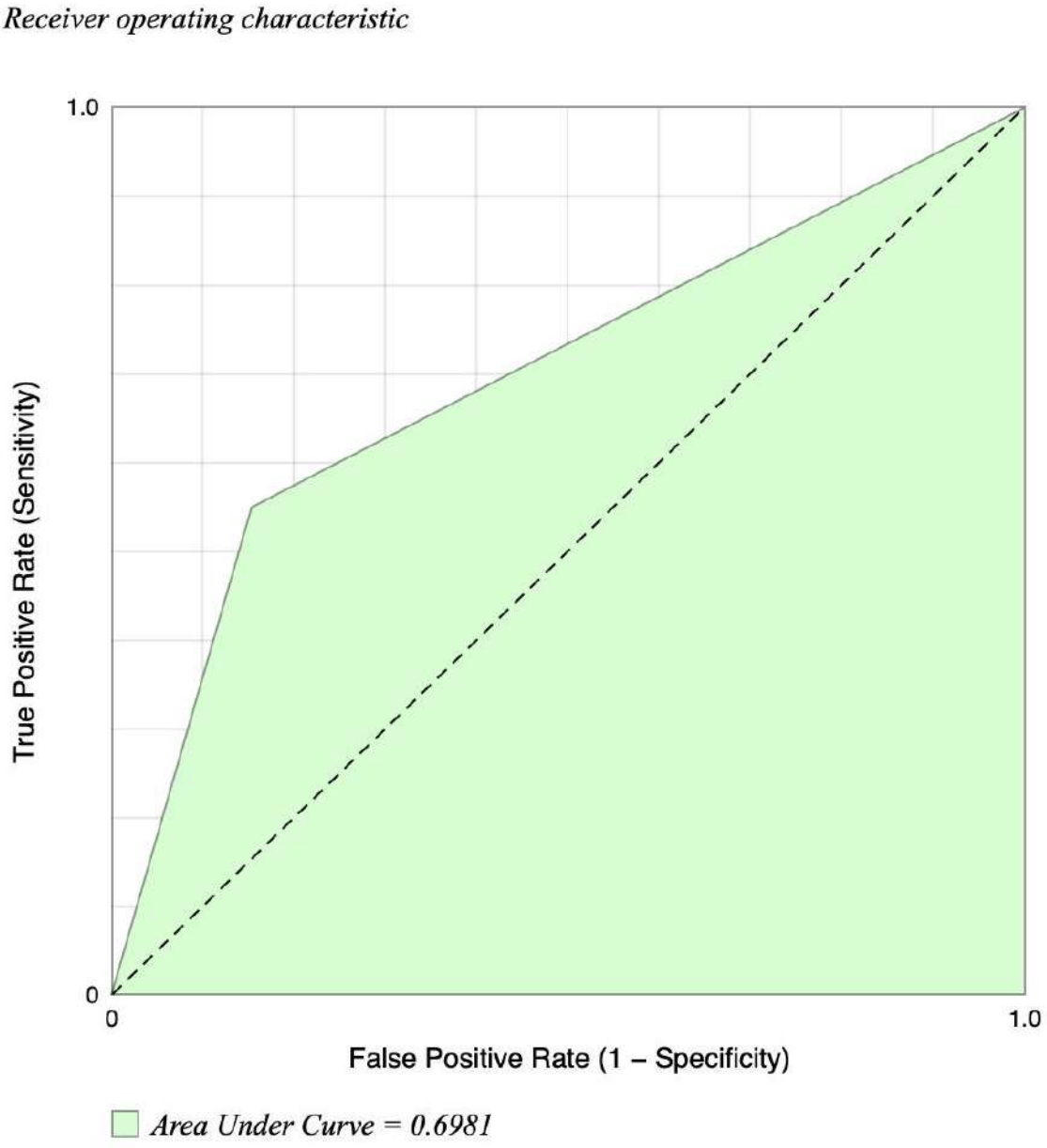


Figure 37 – Receiver operating curve for VIRADS 3, 4, 5

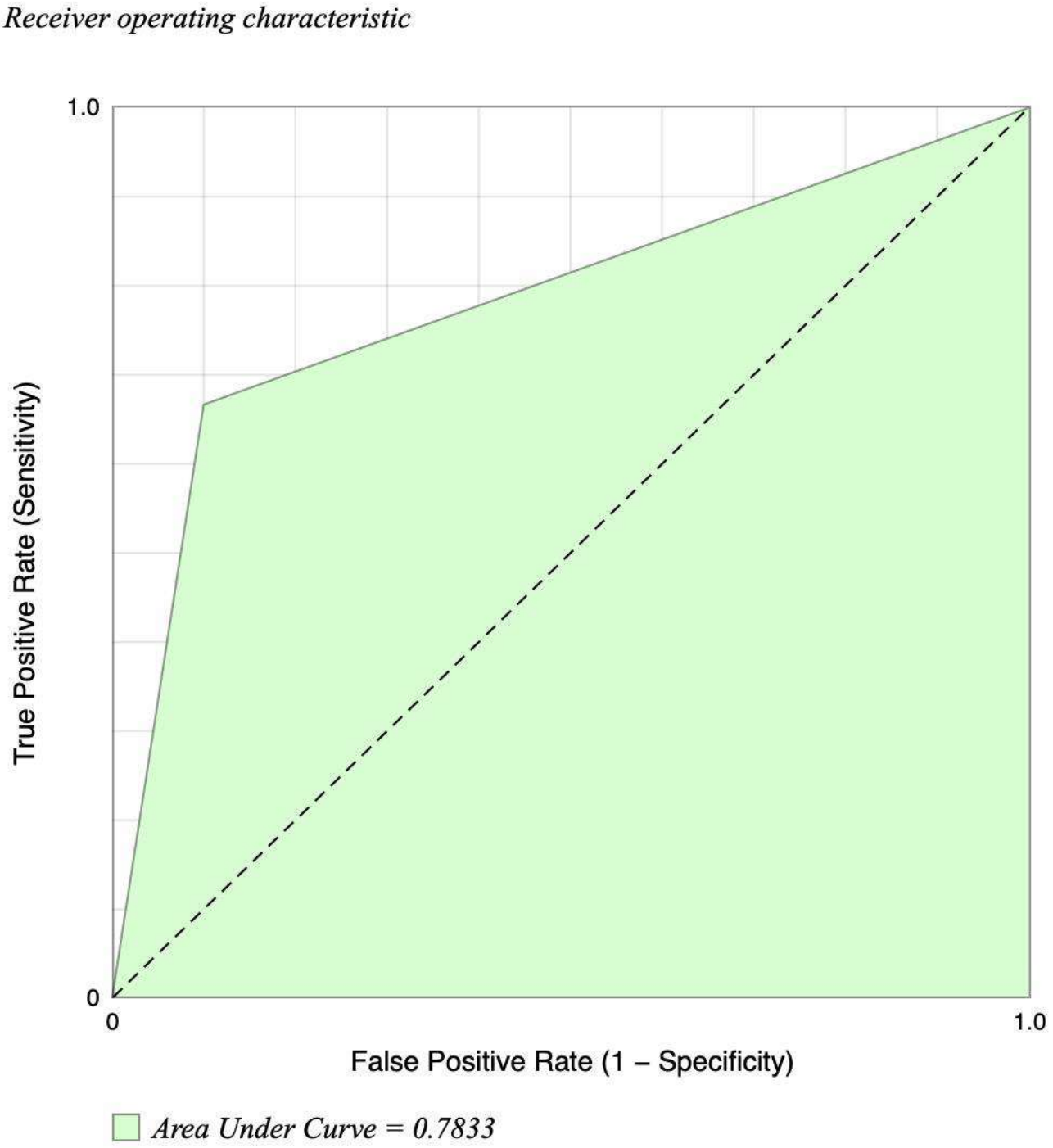


Figure 38 – Receiver operating curve for VIRADS 4, 5

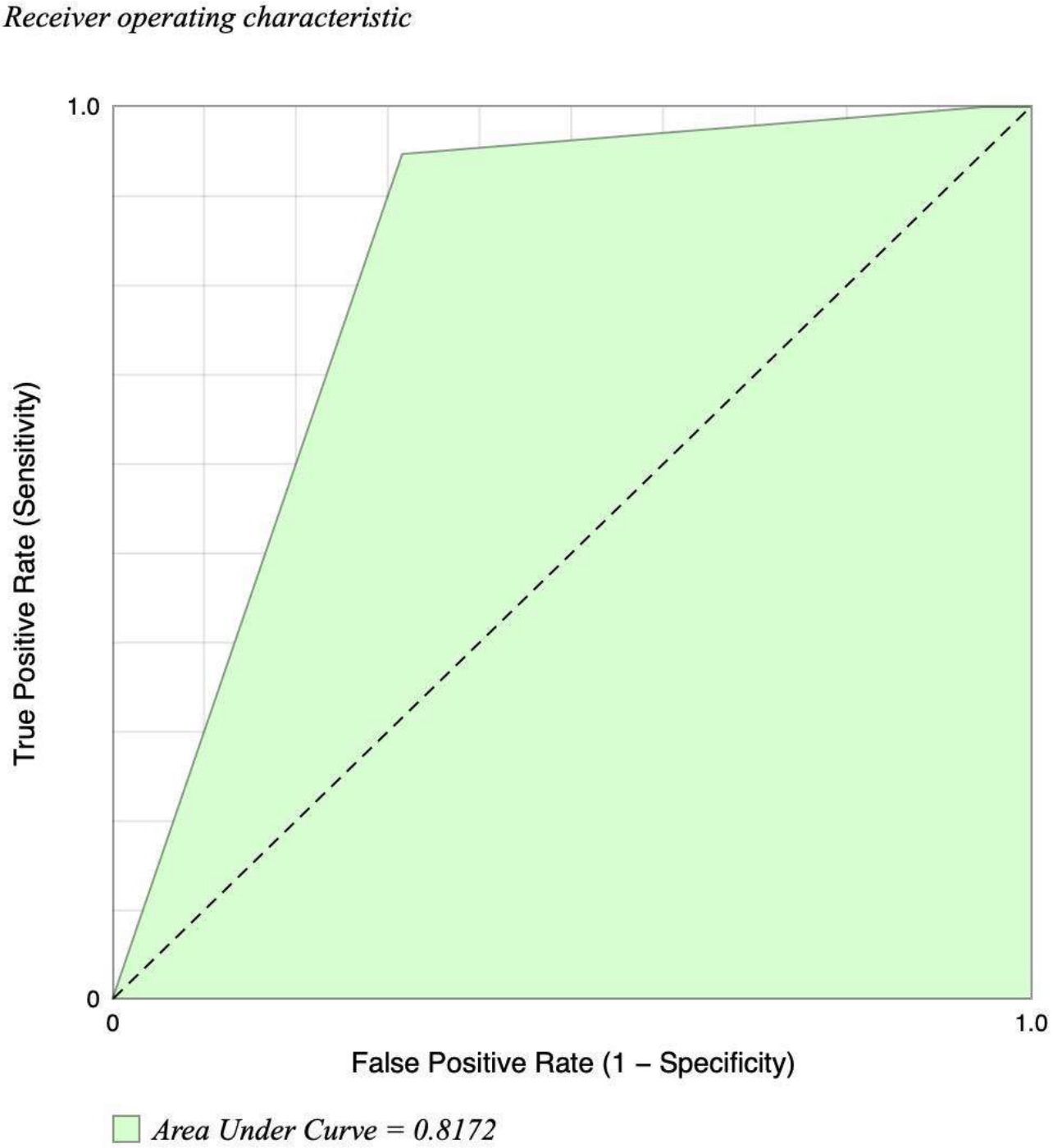
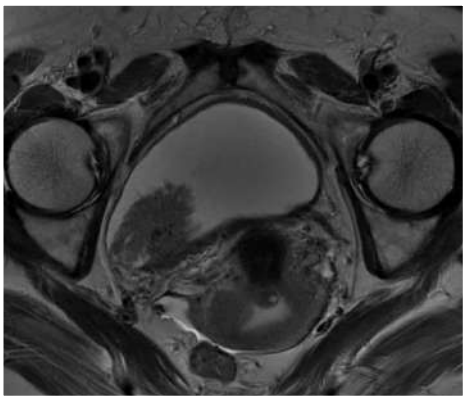


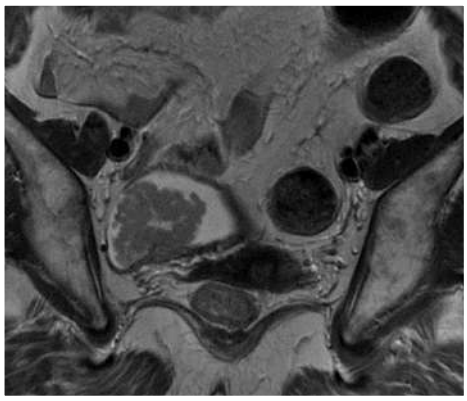
Figure 39– Receiver operating curve for VIRADS 5

The images below depict multiparametric MRI (mpMRI) scans evaluated using the Vesical Imaging Reporting and Data System (VIRADS). These images utilize various MRI sequences, including T2-weighted, Diffusion-Weighted Imaging (DWI), and Dynamic Contrast-Enhanced (DCE) imaging, to assess bladder cancer staging. In mpMRI, the combination of these sequences provides detailed visualization of the bladder wall layers and the extent of tumor invasion. The VI-RADS scoring system, reflected in these images, categorizes the likelihood of muscle-invasive bladder cancer, ranging from scores of 1 (low likelihood) to 5 (high likelihood). These mpMRI VI-RADS images are essential for guiding clinical decisions, offering a comprehensive assessment of the tumor's characteristics, depth of invasion, and involvement with surrounding tissues.

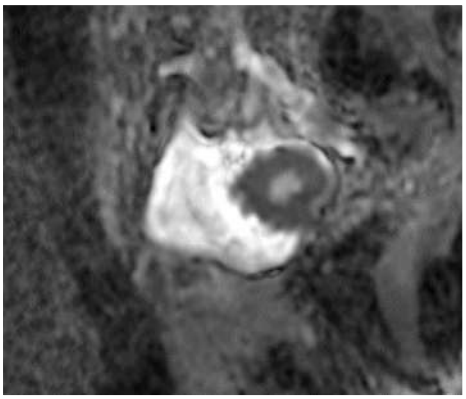
VIRADS 2



T2- W Axial



T2-W Axial



DWI- Saggital

Figure 40- mpMRI VIRADS classification according to T2WI, DWI.

Structural category	2
Contrast enhanced category	2
Diffusion weighted category	2
VIRADS	2

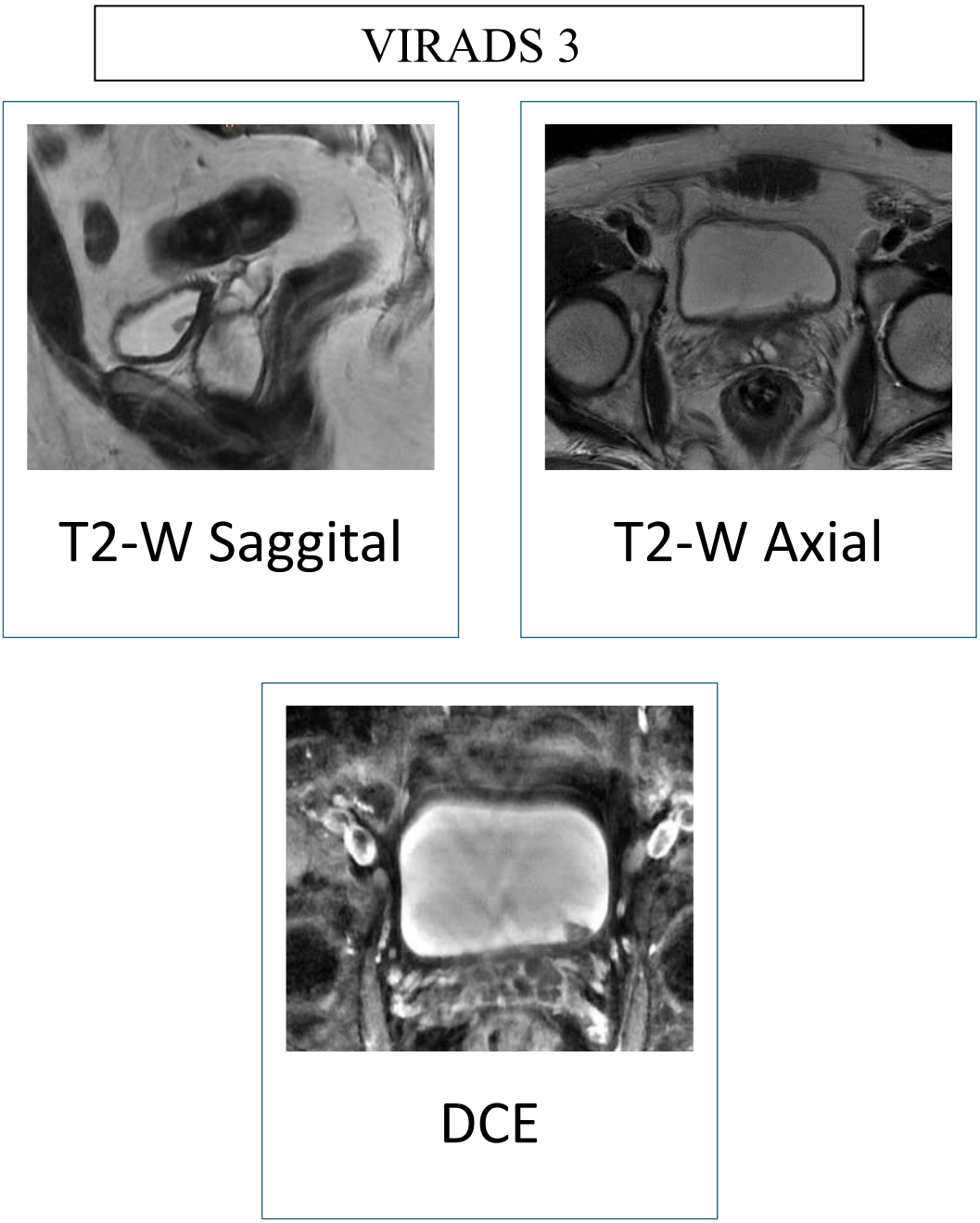
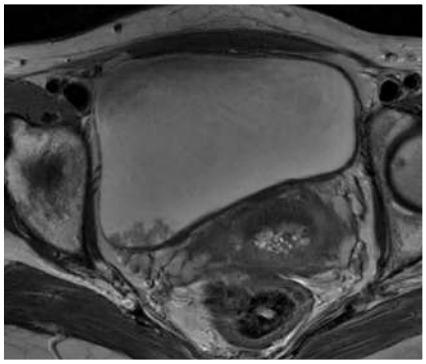


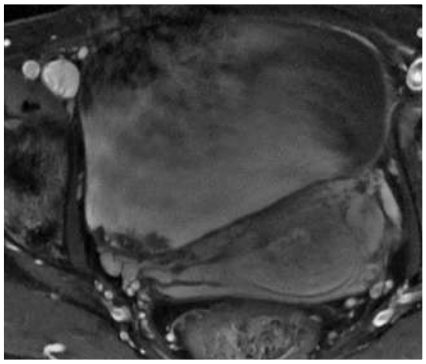
Figure 41- mpMRI VIRADS classification according to T2WI, DCE.

Structural category	2
Contrast enhanced category	1
Diffusion weighted category	3
VIRADS	3

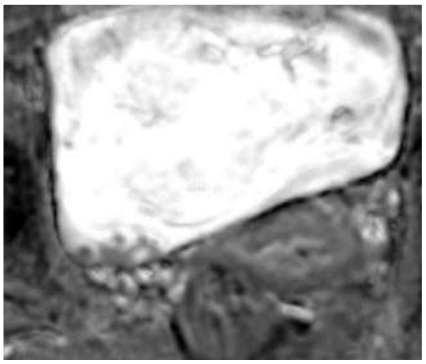
VIRADS 2



T2-W Axial



DCE



DWI

Figure 42- mpMRI VIRADS classification according to T2WI, DWI, and DCE-MRI

Structural category	2
Contrast enhanced category	1
Diffusion weighted category	2
VIRADS	2

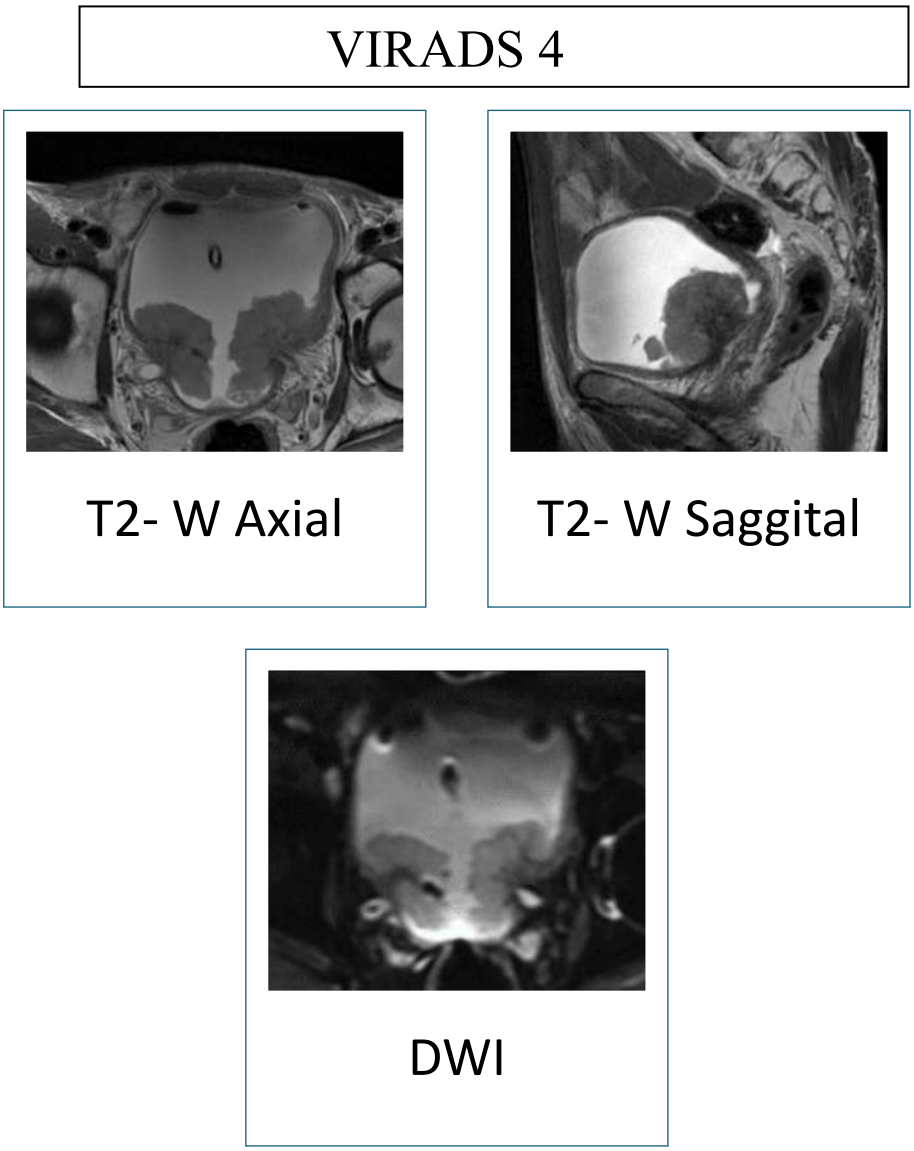


Figure 43 - mpMRI VIRADS classification according to T2WI, DWI.

Structural category	5
Contrast enhanced category	4
Diffusion weighted category	4
VIRADS	4

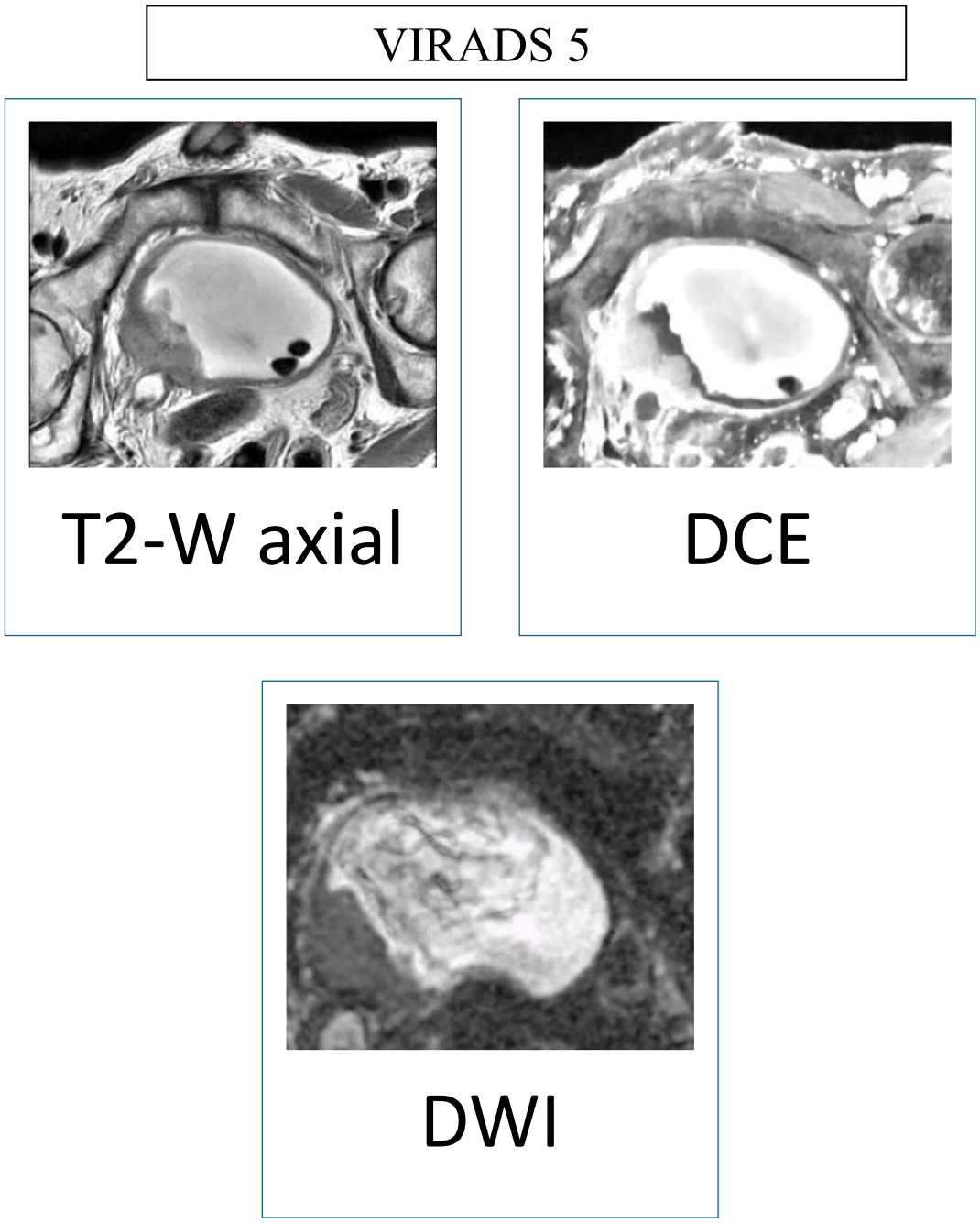


Figure 44- mpMRI VIRADS classification according to T2WI, DWI, and DCE-MRI.

Structural category	5
Contrast enhanced category	5
Diffusion weighted category	5
VIRADS	5

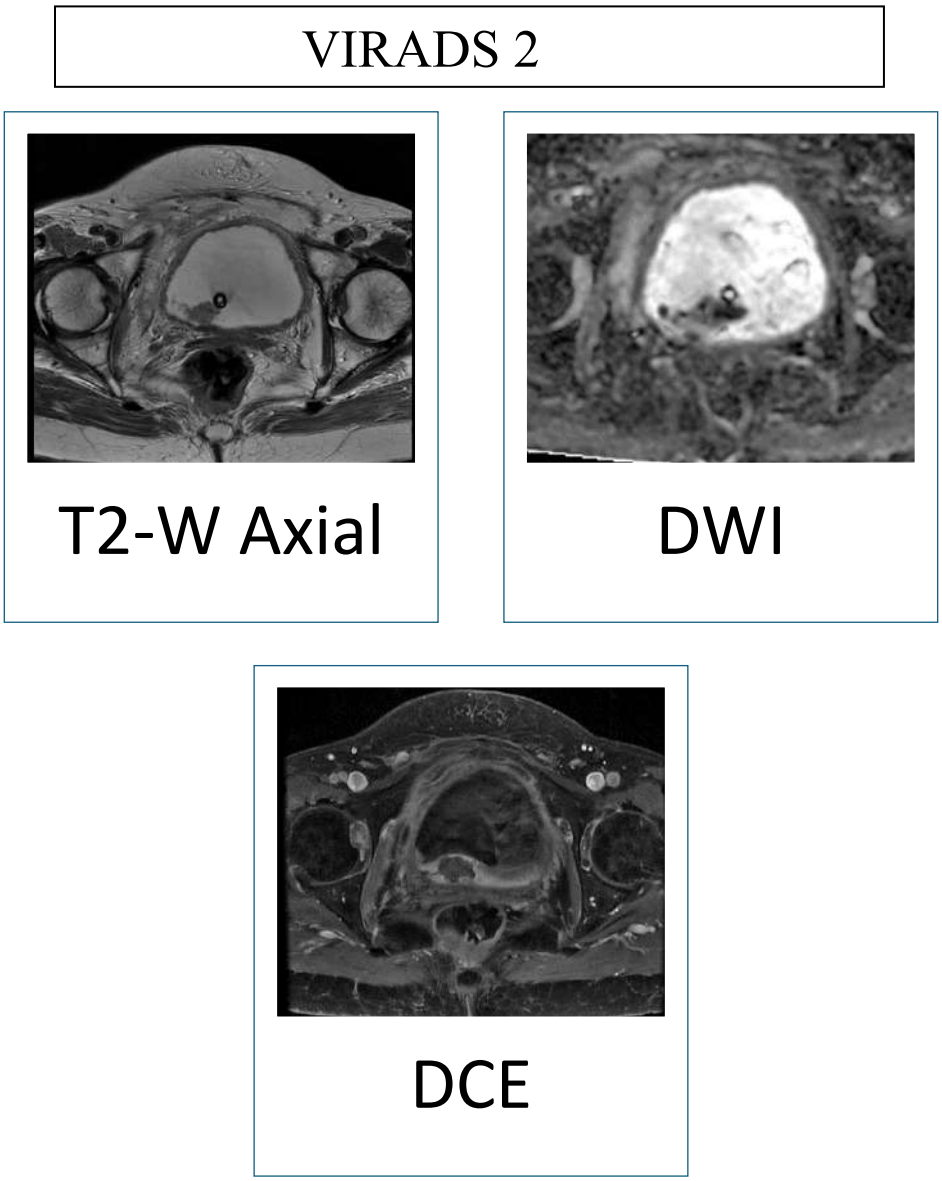
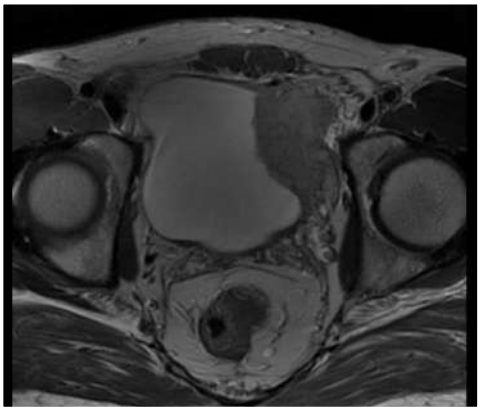


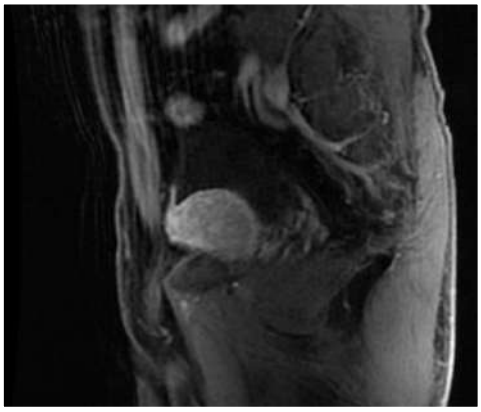
Figure 45- mpMRI VIRADS classification according to T2WI, DWI, and DCE-MRI.

Structural category	2
Contrast enhanced category	2
Diffusion weighted category	2
VIRADS	2

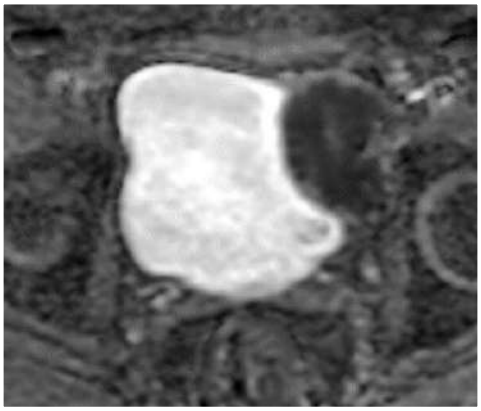
VIRADS 5



T2-W Axial



DCE

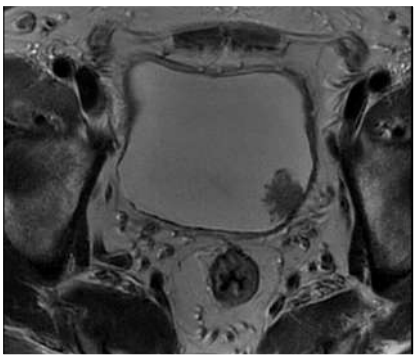


DWI

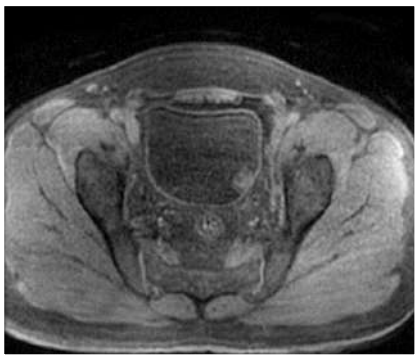
Figure 46- mpMRI VIRADS classification according to T2WI, DWI, and DCE-MRI.

Structural category	5
Contrast enhanced category	5
Diffusion weighted category	5
VIRADS	5

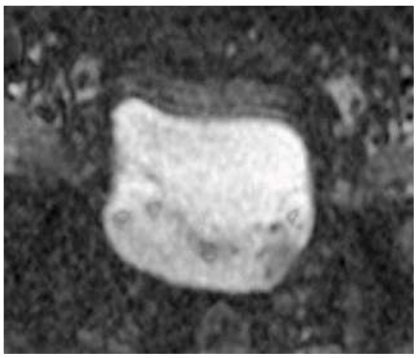
VIRADS 4



T2-W Axial



DCE



ADC

Figure 47- mpMRI VIRADS classification according to T2WI, DWI, and DCE-MRI.

Structural category	4
Contrast enhanced category	4
Diffusion weighted category	4
VIRADS	4

Histopathological Analysis of Bladder Cancer

Detailed Microscopic Images :

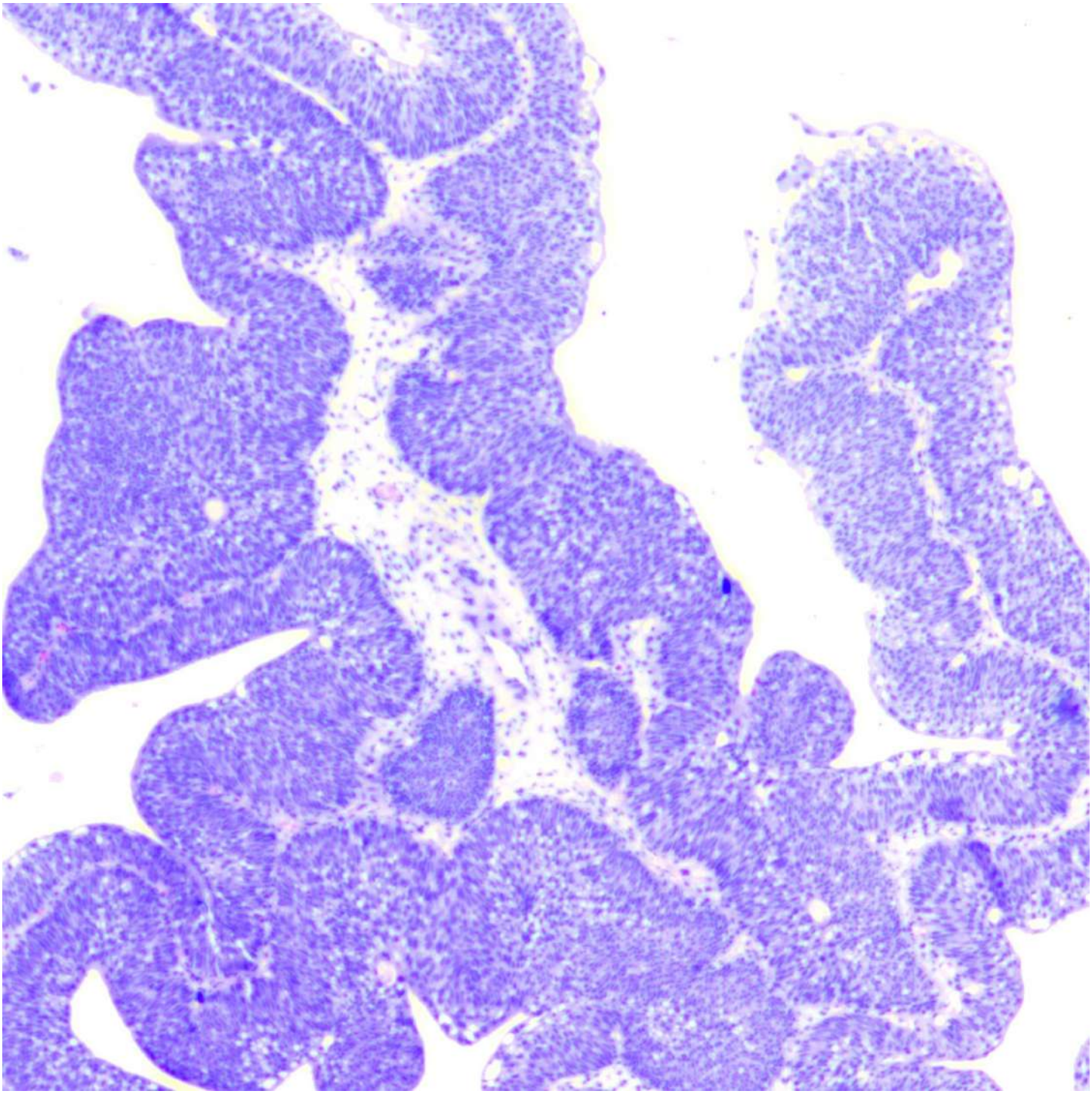


Figure 48-Urothelial Papilloma with papillae having central fibro vascular core lined by urothelial cells and prominent umbrella cell layer (HE, 40x)

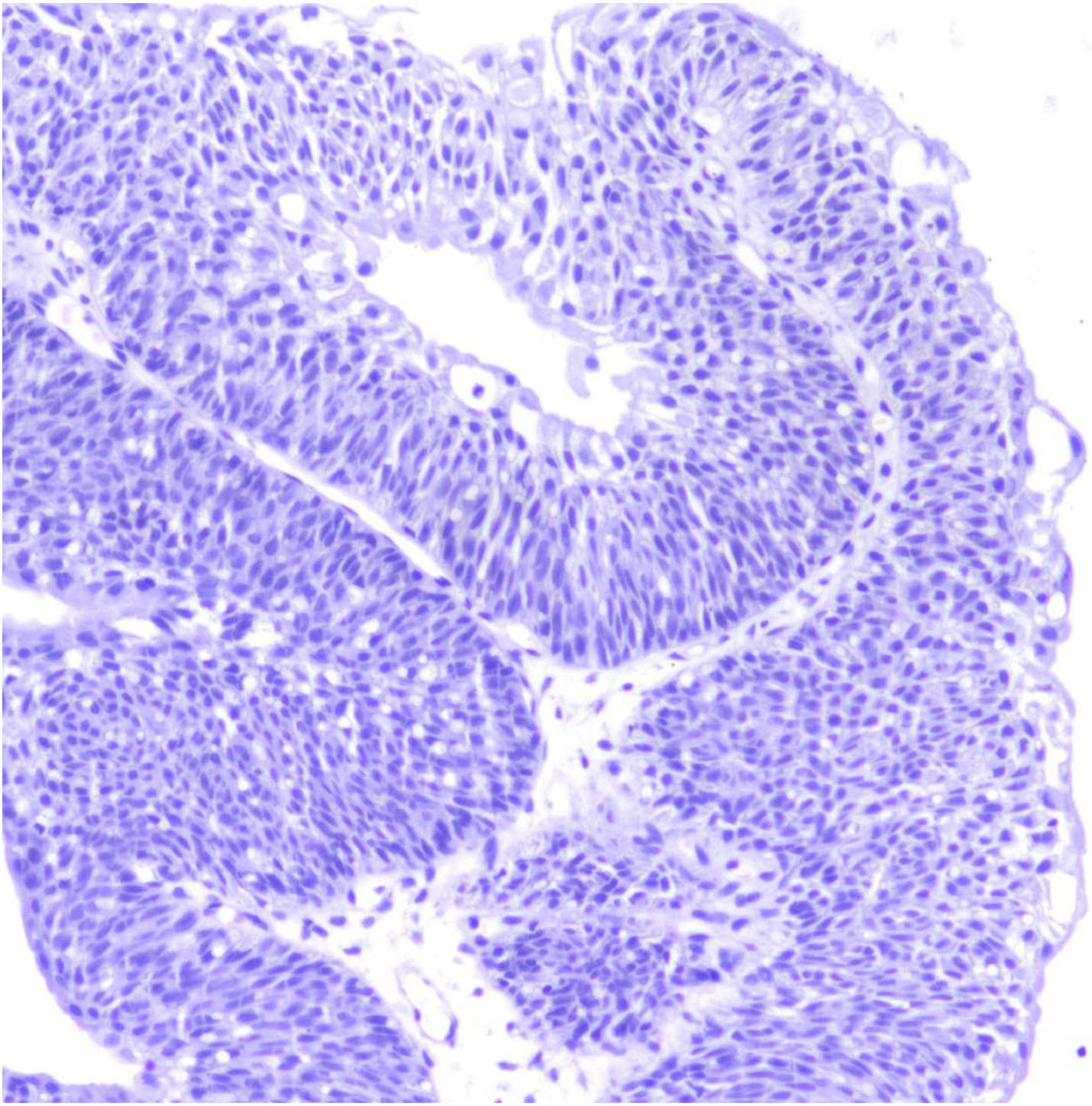


Figure 49-Urothelial papilloma with normal urothelial lining and prominent umbrella cell layer, showing vacuolization (HE, 100x)

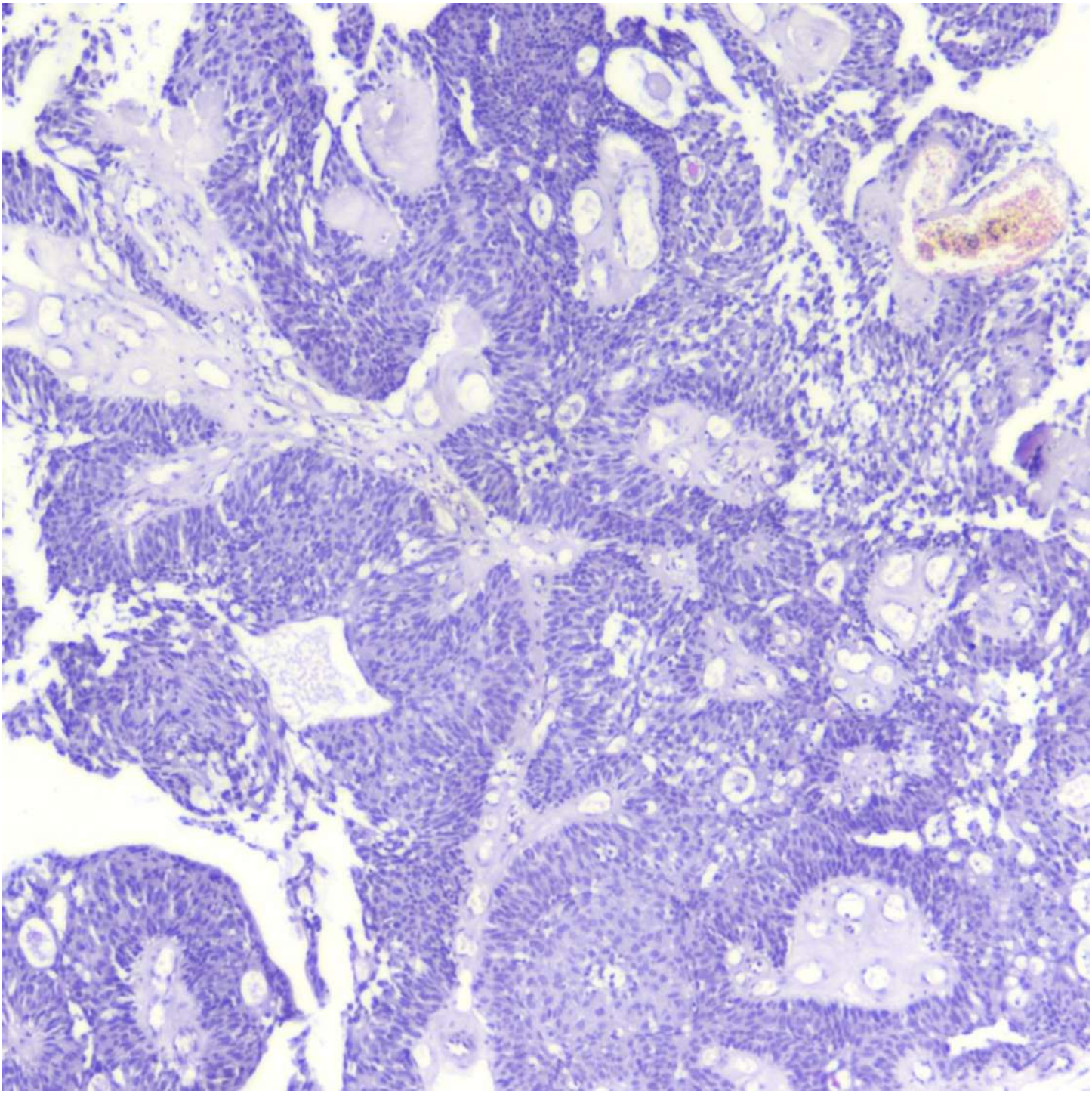


Figure 50-Low grade non- invasive urothelial carcinoma with orderly architecture some loss of polarity and mild pleomorphic (HE, 40x)

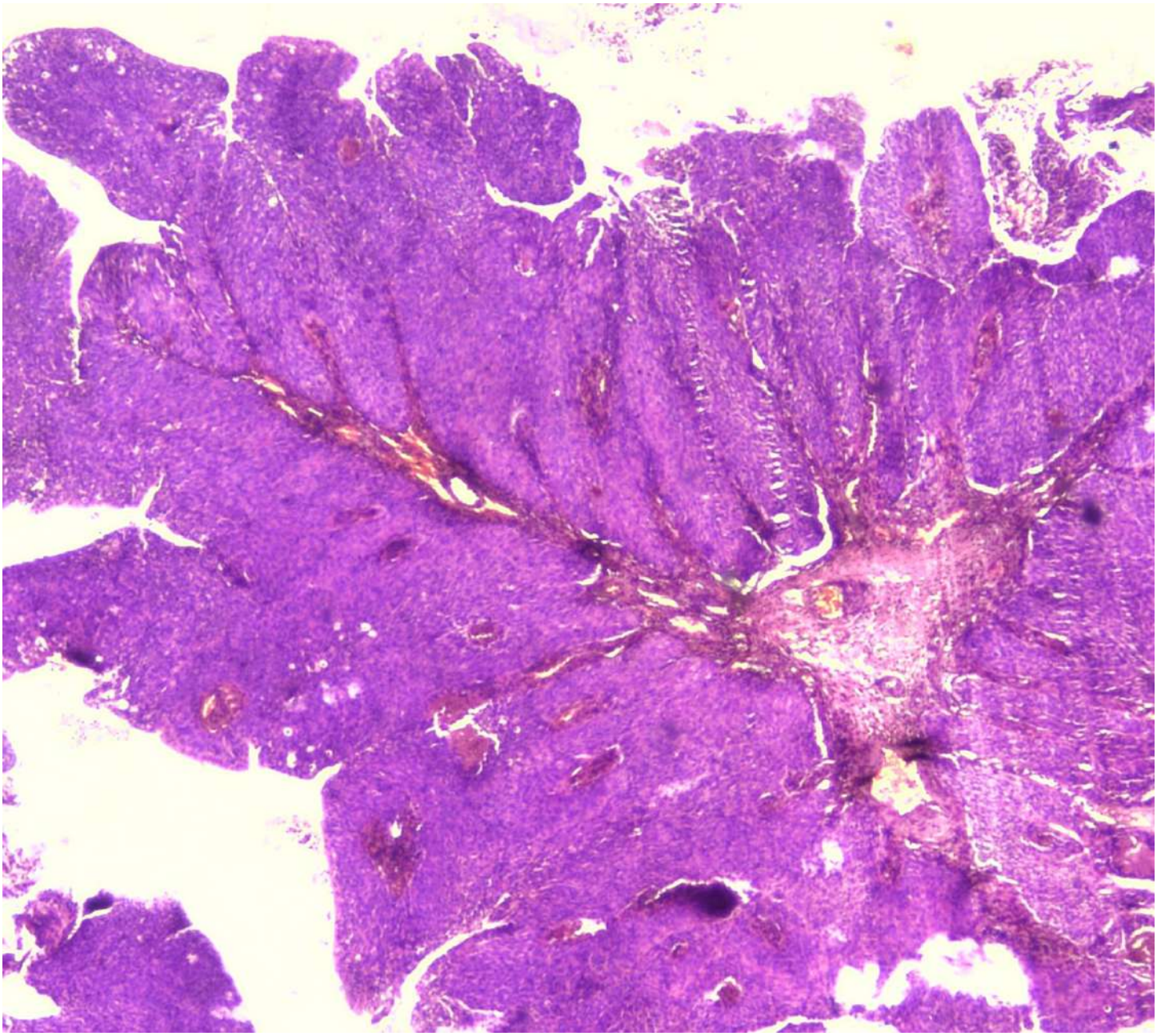


Figure 51-High grade non- invasive urothelial carcinoma with complex papillae (HE, 20X)

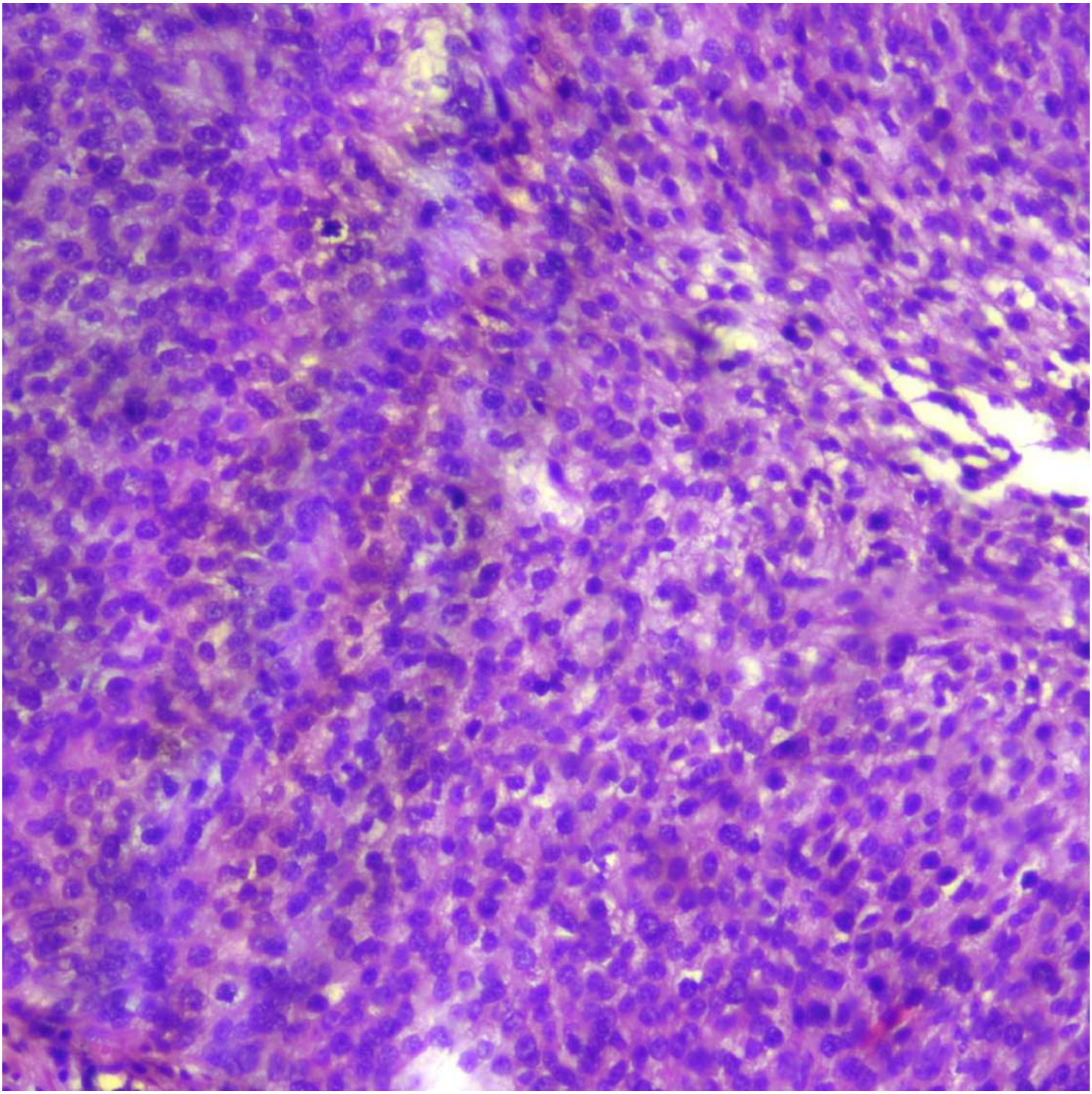


Figure 52-High power of the same showing loss of polarity, nuclear pleomorphic and mitosis in high grade papillary carcinoma (HE, 100x)

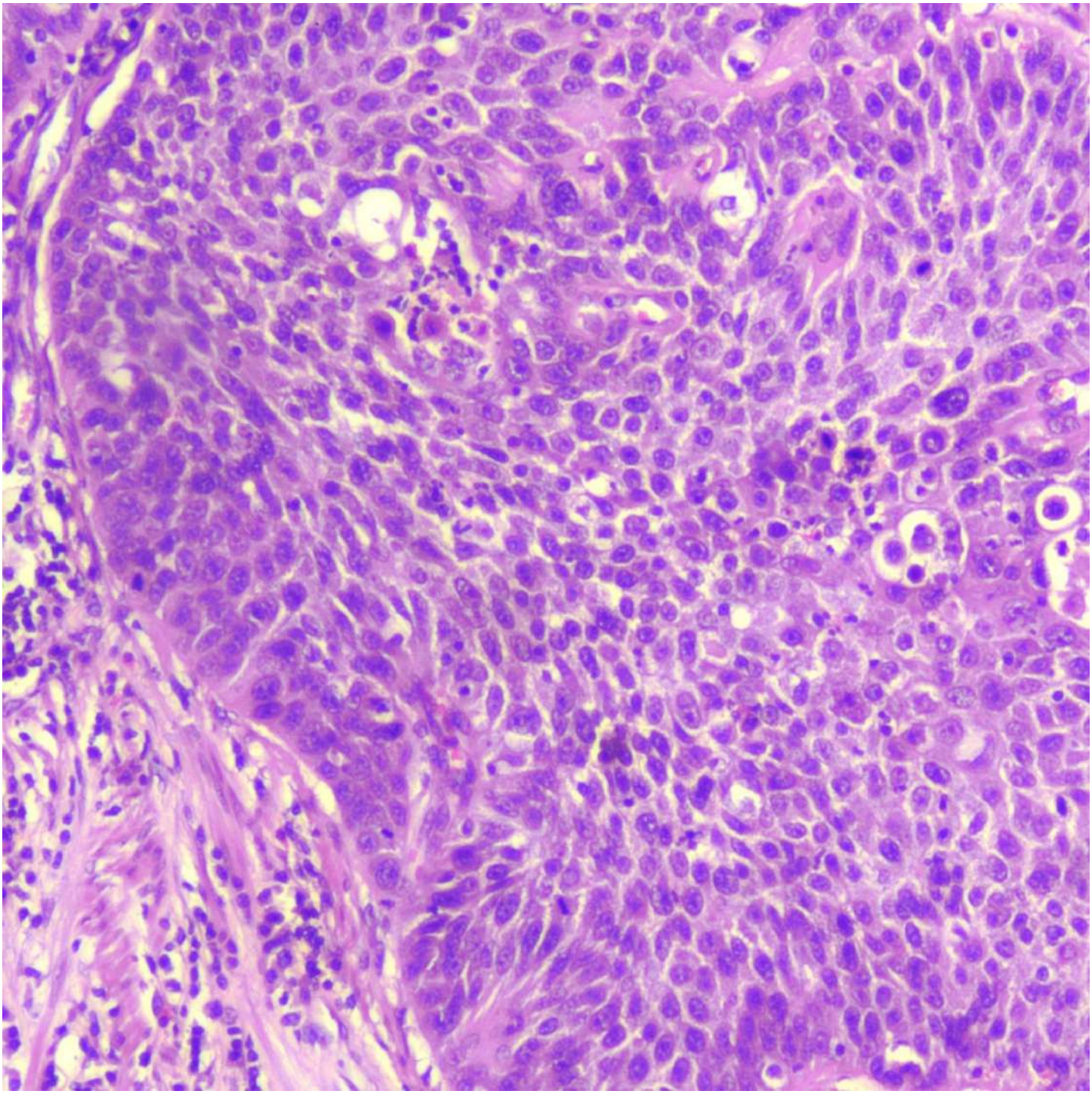


Figure 53-High grade invasive carcinoma with nests of cells showing marked pleomorphic, nuclear atypical and mitosis (HE, 100x)

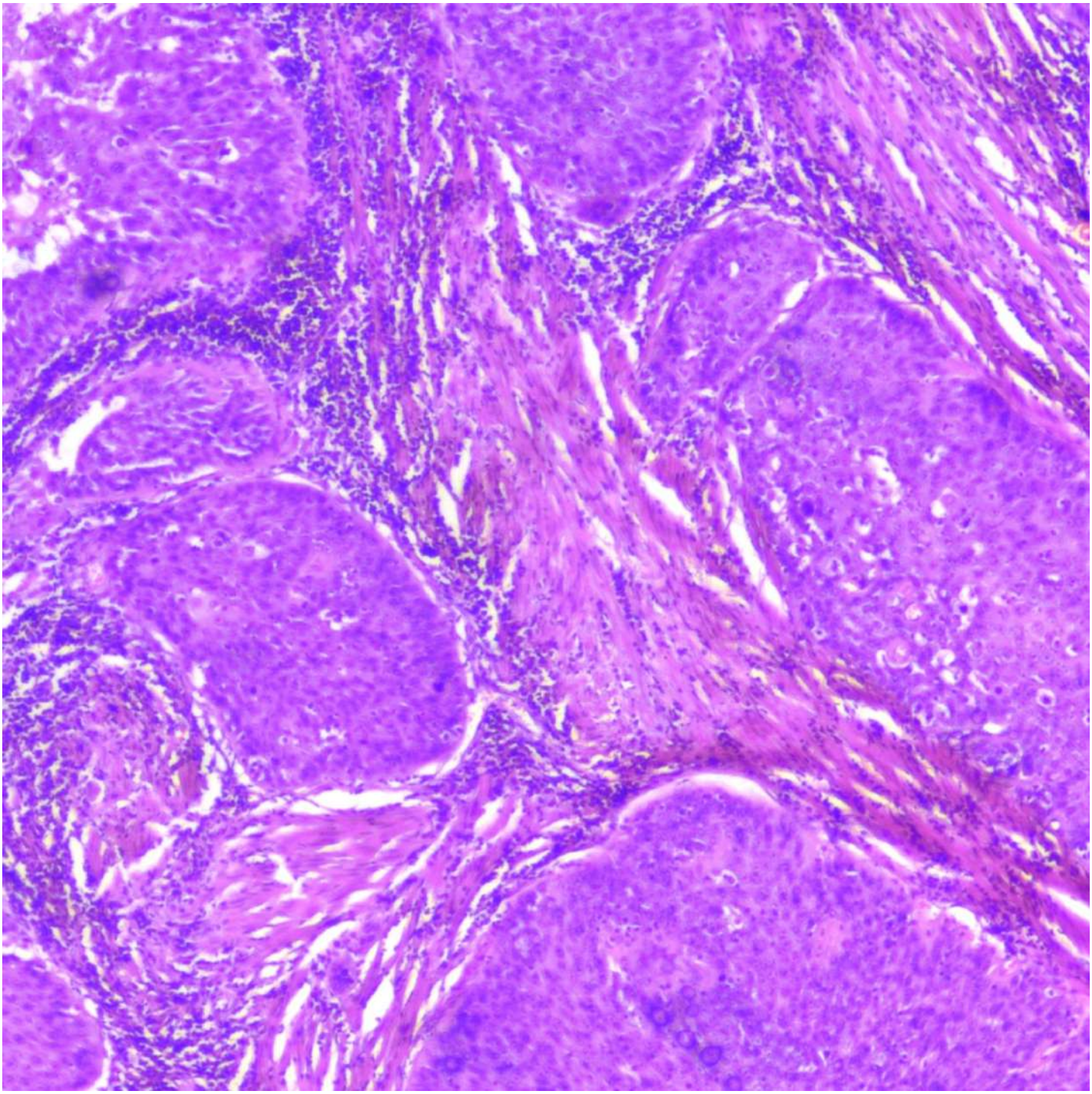


Figure 54-Invasion of muscularis propria by high grade urothelial carcinoma (HE, 40x)

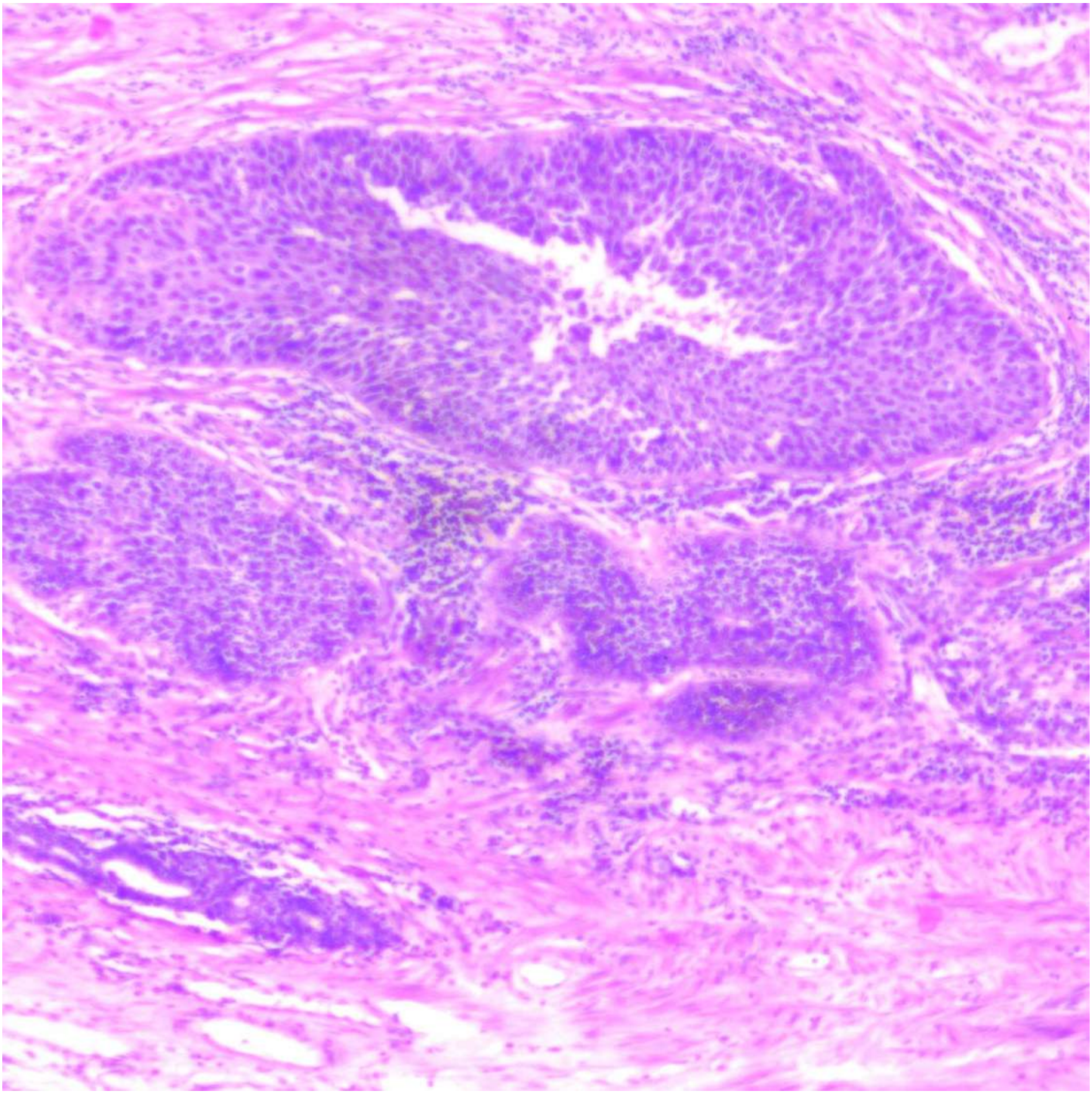


Figure 55-Urothelial carcinoma with invasion of muscularis propria (HE, 40x)

DISCUSSION

The importance of accurate preoperative diagnosis of detrusor muscle invasion in bladder cancer, underscores that non-muscle-invasive bladder cancers (stage T1 or lower) and muscle-invasive bladder cancers (stage T2 or higher) require different treatment approaches. The Vesical Imaging-Reporting and Data System (VIRADS) is highlighted as a tool designed to assess the likelihood of muscle invasion using a five-point scoring system based on MRI.

Bladder cancer has historically lacked suitable imaging techniques for local staging, primarily due to difficulties in obtaining sufficient spatial resolution to differentiate the bladder wall layers, which is crucial for assessing the depth of tumor infiltration. However, with modern imaging techniques with better resolution, mp-MRI bladder has become more prominent before undergoing TURBT.

Distribution of the participants in terms of 'Age (Years)

The average (standard deviation) age of the patients in our research was 62.15 (12.52). The middle value (interquartile range) for the age of the patients was 61.00 (55-72), and the age range of the patients was 23-84 years.

Michele Marchioni [57]performed a study on 38 patients, the median age was 72.5 years (IQR, 66.5-81.0 years).

Yoshiko Ueno et. al[74] included 72 patients of which median age was 73 years (63-83)

Compared to these studies, our study included much younger patients with bladder mass. The youngest patient included in our study was 23 years of age.

The percentage of patients <40 years presenting with bladder tumour was 13% in our study, which was higher than previous reported studies, probably due to higher exposure to smoking and heavy metals in north india.[86]

Distribution of the participants in terms of 'Gender.'

In our study, 53 patients were included, of which 46 were men, and 7 were women.86.8% of the participants had gender: male. 13.2% of the participants had gender: female.

Yoshiko Ueno et. al[74] analyzed 91 patients, of which 72 were men and 19 were women.

Ziyong Wang et al [75] Analysed 220 patients, 194 were males (88.18%) and 26 were females (11.82%).

Wang[7] **et al** conducted a study on 340 patients, of which 294 were males and 44 were females.

Our study similarly showed a similar percentage of males and females who underwent mp-MRI bladder.

Distribution of the participants in terms of 'VIRADS'

In our patient group 3 patients had VIRADS 1, 8 patients had VIRADS 2, 16 had VIRADS 3, 16 had VIRADS 4 and 19 had VIRADS 5.
5.7% of the participants had VIRADS 1. 15.1% of the participants had VIRADS 2. 13.2% of the participants had VIRADS 3. 30.2% of the participants had VIRADS 4. 35.8% of the participants had VIRADS 5.
Huanjun Wang et al[7] included 340 patients, of which 29 had VIRADS 1, 228 had VIRADS 2, 27 had VIRADS 3, 22 had VIRADS 4, and 34 had VIRADS 5.

Ural Oğuz et al[76] included 64 patients, of whom one had VIRADS 1, 26 had VIRADS 2, and 29 had VIRADS 3, 5, 4 had VIRADS 5, and 3 had VIRADS 5.

Ziyong Wang et al[75] included 220 patients, of which 25 had VIRADS 1, 58 had VIRADS 2, 36 had VIRADS 3, 36 had VIRADS 4, and 62 had VIRADS 5.

Our study included a more significant percentage of VIRADS 5 than previous studies, which showed more substantial numbers of VIRADS 2 and 3 category bladder tumors.

Distribution of the participants in terms of 'Largest Dimensions (cm)'

In our group of patients, the average (standard deviation) of the most important measurements (in centimeters) was 3.90 (2.33). The middle value (interquartile range) of the most important measurements was 3.30 cm (with a range of 2-5.3). The greatest measurements ranged from 0.5 to 10.4 cm.

Michele Marchioni et al[57] included 340 patients – which showed the largest dimension of 4cm and a mean size of 1.56cm(5mm-4.6cm)

Giovanni Barchetti et al[10] included 78 patients – which showed the median size of 1.5cm (1.2–2.6cm)

Bladder cancer patients who were involved in our research, the majority of them had large size tumors. Our study revealed a wider range of bladder tumor sizes than what had been reported in previous studies.

Distribution of the Participants in Terms of 'T Stage'

In our patient group, one patient had T0 stage 1, 15 patients had Ta stage, 13 had T1 stage, and 24 had T2 stage.

1.9% of the participants had T Stage: T0, 28.3% had T Stage: Ta, 24.5% had T Stage: T1, and 45.3% had T Stage: T2.

Huanjun Wang et al[7] included 340 patients in which histopathology showed Ta, 31 (9.1%); T1, 224 (65.9%); T2, 64 (18.8%); T3, 15 (4.4%); and T4, six (1.8%) patients, which included more no. of NMIBC patients.

Yoshiko Ueno et al[74] reported histopathology to be-Ta in 29 (31.9%), T1 in 14 (15.4%), and T2 or higher in 48 (52.7%) which showed similar results.

Ziyong Wang et al[75] showed final histopathology report to be: Ta, 3 (1.3%); T1, 104 (41.30%); T2, 56 (25.4%); T3, 53 (24.90%); and T4, 4 (1.8%), showed a similar number of NMIBC and MIBC patients.

Distribution of the Participants in Terms of 'Invasion'

Of our patients, 24 patients had muscle-invasive bladder cancer, and 29 had non-muscle-invasive bladder cancer.

45.3% of the participants had Muscle Invasive bladder cancer, 54.7% of the participants had non-Muscle Invasive bladder cancer

A study conducted by **Huanjun Wang and colleagues** included 340 patients, with 255 (75.0%) diagnosed with non-muscle invasive bladder cancer and 85 (25.0%) diagnosed with muscle-invasive bladder cancer.[7]

Ural Oğuz and colleagues study comprised 80 patients, with 64 (80%) having non-muscle invasive bladder cancer and 16 (20.0%) having muscle-invasive bladder cancer.[76]

In **Michele Marchioni's** study, 68 patients were included, with 61 (89.7%) diagnosed with non-muscle invasive bladder cancer and 7 (10.3%) diagnosed with muscle-invasive bladder cancer.[57]

Compared to these studies, our study showed an almost equal distribution of NMIBC and MIBC, which included a higher number of NMIBC patients.

Distribution of the Participants in Terms of 'Grade'

In our study group, 23 patients had low-grade, and 29 had high-grade urothelial cancer. 44.2% of the participants had low grade. 55.8% of the participants had a high grade bladder cancer.

Huanjun Wang et al[7] included 340 patients - 153 (45.0%) had low-grade cancer, and 187 (55.0%) had high-grade bladder cancer, which showed similar distribution as our study.

Ural Oğuz et al[76] included 80 patients - 64 (80%) had low-grade and 16 (20.0%) high-grade bladder cancer, with an enormous no. of low-grade bladder patients.

Michele Marchioni et al [57]**included** 68 patients - 42(61.8%) had low-grade, and 26(38.2%) had high-grade bladder cancer; they also showed a more significant no. of low-grade bladder cancer patients as compared to our study.

Distribution of the Participants in Terms of 'Lesion Number'

In our study group, 42 patients had a single lesion present, and 11 had multiple bladder growths.

79.2% of the participants had a single lesion. 20.8% of the participants had multiple lesions.

Huanjun Wang et al[7] Included 340 patients - 283 (83.2%) had low-grade cancer, and 57 (20.1%) had high-grade bladder cancer, which showed similar distribution as our study.

Association Between 'VIRADS' and 'Grade'

The analysis in our research utilized Fisher's exact test to investigate the connection between 'VIRADS' and 'Grade.' We observed a notable distinction in Grade distribution among the different groups ($\chi 2$ = 26.623, p = <0.001). The strength of the association between these two variables, as indicated by the Bias Corrected Cramer's V, was 0.66 (indicating a high association).

Ziyong Wang[75] **and colleagues** found that there was a higher frequency of high-grade tumors associated with higher VI-RADS scores. They also discovered a statistically significant relationship between high VI-RADS scores (4 and 5) and high-grade bladder cancers, although the correlation with tumor stage was stronger.

Our study showed robust association between VIRADS and higher grade of tumor, similar to this study.

Del Giudice[50] **and co-authors** reported that multiple studies indicated a moderate correlation between high VI-RADS scores and high-grade tumors. They suggested that VI-RADS should primarily be used for staging, as it showed a weaker association with grade compared to its strong correlation with muscle invasion.

This was different from our study, which showed a strong association of VIRADS score with the grade of the tumor.

Fujii and team[53] demonstrated that patients with high-grade bladder cancer were more likely to have VI-RADS scores of 4 and 5. They also noted that there were cases of high-grade bladder cancer with low VI-RADS scores, particularly in non-muscle-invasive tumors. The study

emphasized that while VI-RADS effectively detected the T stage, its association with grade was not strong enough to be relied upon for grading decisions.

The findings in our research differed from those in the study, as we observed a significant correlation between the VIRADS score and the tumor grade.

Association between 'T Stage' and 'Largest dimensions (cm)'

In our research, we found a notable distinction among the four groups regarding the largest dimensions (cm) ($\chi 2 = 17.437$, $p = 0.001$). The T Stage: T2 group had the highest median largest dimensions (cm).

Kassouf and colleagues[77] discovered a significant association between larger tumors (≥3 cm) and an increased risk of progressing to muscle-invasive bladder cancer (T2 or higher), showing similar association of large size of tumour to degree of invasion.

Margulis et al[78] demonstrated that tumors larger than 3 cm were significantly linked to higher T stage (T2–T4) and poorer survival outcomes.

Our research findings also indicated that larger tumor size was associated with a higher T stage.

Shariat et al[79] conducted a study that revealed a higher frequency of advanced T stages (T3 and T4) in tumors larger than 5 cm compared to smaller tumors. Based on our research, we also found that a greater tumor size was linked to a higher T stage.

Association Between 'T Stage' and 'Grade'

Our research utilized the Chi-squared test to examine the relationship between 'T Stage' and 'Grade.' A significant difference was found in Grade distribution among the different groups ($\chi 2 = 31.857$, $p = <0.001$). The strength of the association between the two variables (Cramer's V) was calculated to be 0.78.

Sylvester et al[80] found that high-grade non-muscle-invasive bladder cancer (NMIBC), particularly T1 high-grade tumors, had a significantly higher probability of progressing to muscle-invasive disease (T2 or higher) compared to low-grade NMIBC.

Our research was in line with this study showing high grade tumours tend to be more invasive.

Shariat et al[81] reported that high-grade bladder tumors were notably more likely to become muscle-invasive and were associated with poorer overall survival compared to low-grade tumors.

Our study also provided a similar association of high-grade tumors with higher stages of the tumor.

Kamat et al[82] conducted research that revealed that high-grade T1 bladder cancers had a higher likelihood of advancing to muscle-invasive disease (T2 or higher) compared to low-grade T1 tumors. Additionally, high-grade T1 tumors were considered more aggressive and were associated with an increased risk of progressing to deeper bladder layers, leading to poorer clinical outcomes.

Our research also found a comparable link between high-grade tumors and more advanced stages of the bladder cancer.

Association Between 'T Stage' and ' Hydronephrosis'

We utilized **Fisher's exact test** in our research to investigate the relationship between 'T Stage' and Hydronephrosis. We observed a noteworthy difference in the distribution of any Hydronephrosis among the different groups ($\chi 2 = 11.672$, $p = 0.003$). The strength of association between the two variables (Cramer's V) was determined to be 0.47, indicating a moderate association. Additionally, the bias corrected Cramer's V value was calculated to be 0.41, also indicating a moderate association.

Nishikawa et al[83] in their study showed that Hydronephrosis strongly correlated with the depth of tumor invasion (T stage) and nodal involvement. Patients with Hydronephrosis had worse pathological outcomes and lower overall survival, with comparable outcomes to our study.

Chang et al[84] indicated that hydronephrosis was more prevalent in patients with MIBC (T2 or higher) than those with NMIBC. The presence of hydronephrosis was strongly associated with tumor invasion beyond the bladder muscle (T2–T4) and was an independent predictor of worse disease-free survival and overall survival, as our study provided moderate association between invasion and hydronephrosis.

Kikuchi et al[85] in their study found that patients with hydronephrosis were more likely to have T3 or higher bladder cancer. Hydronephrosis was an independent predictor of pathological upstaging and poorer overall survival, providing comparable outcomes.

PERFORMANCE STUDY OF PARAMETERS

A VIRADS 3 cut-off for predicting detrusor muscle invasion yielded a sensitivity of 100%, specificity of 27.5%, PPV of 31%, NPV of 100%, and diagnostic accuracy of 45.3%.

A VIRADS 4 cut-off for predicting detrusor muscle invasion yielded a sensitivity of 100%, specificity of 62.1%, PPV of 68.6%, NPV of 100%, and accuracy of 79.2%.

A VIRADS 5 cut-off for predicting detrusor muscle invasion yielded a sensitivity of 75%, specificity of 96.6%, PPV of 94.7%, NPV of 82.4%, and diagnostic accuracy of 86.8%.

One of the patients who presented in the VIRADS 5 category, indicating a high risk of bladder cancer, was initially diagnosed with T1 tumor. However, upon further analysis of the histopathology specimen after radical cystectomy, it was determined that the patient actually had muscle-invasive bladder cancer. This change in diagnosis has significant implications for the patient's treatment and prognosis.

In certain patients, even if they are categorized as VIRADS 5, there is a chance that they may be incorrectly labeled as having non muscle invasive bladder cancer due to sampling errors during transurethral resection of bladder tumor (TURBT).

Upon observing this particular scenario, we can make an infer that:

ALL VIRADS 5 LESIONS TEND TO BE MUSCLE-INVASIVE BLADDER CANCER.

Del Giudice et al[50] applied a VI-RADS cutoff of 3 and reported a sensitivity of 91.9%, specificity of 91.1%, and an AUC of 0.94, with a larger sample size (n = 231) compared to the present study (n = 53). The sensitivity and AUC in the present study were higher this study (100%), and its specificity was lower (91.1% vs. 27.5%)

Marchioni et al[57] used a VI-RADS cutoff of 4 to distinguish MIBC from non-muscle-invasive bladder cancer (NMIBC), reporting a sensitivity of 85.7%, specificity of 86.9%, and AUC of 93% with a smaller sample size (n = 38). The present study showed lower specificity (62.1% vs. 86.9%) but lower sensitivity (100% vs. 85.7%) than theirs.

Ueno et al[76] conducted a retrospective study using a VI-RADS cutoff of 3 to predict muscle invasion, reporting a sensitivity of 88%, specificity of 77%, and an AUC of 0.90. For a cutoff of 4, they found a sensitivity of 76%, specificity of 93%, and an AUC of 0.90, with a larger sample size (n = 74) than the present study. They showed higher specificity and lower sensitivity than our study.

Wang et al[75] conducted another retrospective study using a VIRADS cutoff of 3 to indicate muscle invasion, reporting a sensitivity of 87.1%, specificity of 96.5%, and an AUC of 0.94. They showed higher specificity and lower sensitivity than our study.

In a study by Ghanshyam et al[52] a cut-off score of VIRADS ≥4 yielded sensitivity, specificity, PPV, and NPV of 79.4%, 94.2%, 90.0%, and 87.5%, respectively. In our study, VIRADS ≥4 showed a similar sensitivity of 100% and lower specificity of 62.1%, PPV of 68.6%, NPV of 100%, and accuracy of 79.2%. A cut-off score of VIRADS ≥3 in their study showed similar sensitivity (91.2%) but higher specificity (78.8%) as compared to our research.

Barchetti G et al[10] evaluated the effectiveness of VIRADS in differentiating between invasive and non-invasive bladder cancer. When VIRADS >3 was used as the cut-off, sensitivity and specificity were 82% and 94%, respectively, which differed from our study, which showed higher sensitivity with lower specificity.

Nesrin Gunduz et al[56] analyzed 71 patients, accepting VI-RADS ≥3 as predictive of MIBC. Their sensitivity and specificity for detecting MIBC were 75% and 56.4%, respectively, with lower sensitivity and higher specificity compared to our study.

Mustafa Erkoc et al[59] studied 330 patients and set a VIRADS cut-off of >3 to distinguish MIBC from NMIBC. Sensitivity, specificity, PPV, and NPV for all patients were 91.3%, 91.8%, 81.7%, and 96.3%, respectively, with an AUC value of 0.934. Their study had similar sensitivity and higher specificity to our study.

Tarek M El-Karamany et al[60] used a cut-off score of 3, in which VIRADS showed a sensitivity of 78.6%, specificity of 77.8%, PPV of 84.6%, NPV of 70.0%, and accuracy of 78.3%, with lower sensitivity, higher specificity, and higher diagnostic accuracy in their study.

Katerina Rysankova et al[63] showed that in 64 patients, sensitivity was 92.3% and specificity 81.4% with VIRADS ≥3, which was similar to and higher than our study's sensitivity and specificity. In contrast, sensitivity was 76.9% and specificity 91.5% with VIRADS ≥4, which was lower in sensitivity and higher in specificity.

Limitations

Limitations of study

1) This study was limited to a single institution with a small sample size, making it difficult to extend the findings broadly. A larger, multicenter study is suggested for better generalization.

2) mpMRI bladder is costly, cannot be afforded by every patient in India, and is limited to a few centers only.

3) Radiologist training with a steep learning curve is required to prevent intra- and interobserver variability in reporting VIRADS.

3) mpMRI bladder has limited utility in cases presenting with storage LUTS and diagnosed with carcinoma in situ on blue light cystoscopy.

4) Diagnostic accuracy after TURBT in patients with T1 stage who underwent re-TURBT was not included if recurrence occurred.

5) Distribution of patients in various groups-

1) VIRADS 1-3

2) VIRADS 2-8

3) VIRADS 3-7

4) VIRADS 4-16

5) VIRADS 5-19

The percentage of presenting patients in group VIRADS 4 and VIRADS 5 were much higher as compared to other studies. Which prevented us to accurately understand role of VIRADS 1-3 in diagnosing muscle invasive bladder cancer.

Future Prospects

Future Prospects

The future prospects for VIRADS (Vesical Imaging-Reporting and Data System) scoring in bladder cancer diagnosis and management appear promising, with several potential developments and areas of focus:

1. **Wider Adoption and Standardization**

- As VIRADS gains validation in more clinical settings and larger patient cohorts, its wider adoption across medical institutions worldwide is expected. This could lead to standardized protocols for bladder cancer imaging, allowing for more consistent and reliable assessments of detrusor muscle invasion.

2. **Improved Accuracy through Technological Advances**

- Ongoing improvements in MRI technology, including higher-resolution imaging and advanced software for image processing, will likely enhance the precision of VIRADS scoring. Artificial intelligence (AI) and machine learning algorithms could also be integrated to automate and improve the accuracy of score interpretation.

3. **Integration with Other Diagnostic Tools**

- Future research may explore how VIRADS can be integrated with other diagnostic modalities, such as molecular biomarkers, urine cytology, or imaging techniques like PET/CT. Combining VIRADS with these modalities could improve overall diagnostic accuracy, especially in ambiguous cases or distinguishing between aggressive and non-aggressive tumors.

4. **Predictive Value for Treatment Outcomes**

- Studies could further validate the use of VIRADS in predicting the presence of muscle invasion and patient outcomes after treatment, such as recurrence or progression rates. This would position VIRADS as a vital tool in tailoring individualized treatment plans, helping clinicians decide whether to proceed with conservative management or more aggressive interventions like radical cystectomy.

5. **Application in Treatment Monitoring**

- In the future, VIRADS might be used for initial staging and monitoring treatment response in patients undergoing therapies such as chemotherapy or immunotherapy. By tracking changes in the VI-RADS score over time, clinicians could assess how well the tumor responds to treatment and make adjustments as necessary.

6. **Personalized Medicine and Prognostication**

- VIRADS could become a component of personalized medicine strategies, where individual patient risk profiles are developed based on imaging data combined with genetic and clinical information. This could enable more precise prognostication and tailored treatment plans, optimizing outcomes for bladder cancer patients.

7. **Role in Training and Education**

- As the system becomes more entrenched, there will be opportunities to use VIRADS as a training tool for radiologists and urologists, helping improve their ability to assess bladder cancer staging. Educational programs incorporating VIRADS could standardize expertise across institutions, reducing staging and treatment planning variability.

8. **Global Multi-center Studies**

- Future multi-center, international studies will likely further validate the scoring system across patient populations, MRI equipment, and healthcare systems. This global research effort would ensure that VIRADS is applicable and reliable in diverse clinical environment

SUMMARY

The Vesical Imaging-Reporting and Data System (VIRADS**)** was developed to standardize multiparametric MRI (mpMRI) reporting and interpretation in bladder cancer, particularly to assess muscle invasion. The system provides a 5-point scoring scale to predict the likelihood of detrusor muscle invasion (T2 or higher) in bladder cancer.

Our study explores the relationship between VIRADS scoring and muscle invasion, VIRADS scoring to tumor grade, depth of invasion to grade, tumor size, and hydronephrosis.

Bladder cancer is usually seen in the 60-70s age group, but our study also included younger patients in which bladder cancer is uncommon. Previous studies have been performed on older patients, and our study provides insight into VIRADS scoring in the young population.

In our study, as compared to previous studies, male participants presented with bladder mass much more frequently than their female counterparts.

In our study, a larger percentage of patients presented in the VIRADS 4 and 5 group, as compared to previous studies, which showed patients in the VIRADS 2 and 3 category.

This might represent our study population presenting much later due to lack of access to medical care and potentially ignorance of symptoms like hematuria before presenting to the urologist.

Due to their late presentation, our study included much larger bladder masses, the largest of which was 10.3cm. These large bladder masses tend to present at locally advanced stages.

The majority of these tumors in our study were of high grade, and a more significant percentage presented with muscle invasion.

Also, up to 20% of patients in our study presented with multiple bladder tumors, in which the cancer with the highest VIRADS score was used for the analysis of the degree of invasion.

At a higher stage of Tumor (T2), 95% of these patients presented with high-grade tumors. The majority (95%) of NMIBC didn't show hydronephrosis, compared with 45% of MIBC.

In our study, the T stage was positively correlated with the increasing size of the tumor, with an increased stage showing a larger size.

VIRADS 5 score showed good diagnostic accuracy of 87% in detection of muscle-invasive bladder cancer with moderate sensitivity of 75% and high specificity of 96.6%,

The limitations of our study included a smaller sample size, with more patients in the VIRADS 4 and VIRADS 5 categories. Further assessment between radiologists to analyze intra- and interobserver variability would have provided more meaningful insight into the analysis of VIRADS scoring.

CONCLUSION

Our study results suggest that the VIRADS 5 scoring system has high specificity, and positive and negative predictive value to predict muscle invasive bladder cancer. In VIRADS 5 patients, additional randomized controlled studies could be conducted to randomly assign patients to either undergo TURBT or to proceed directly to radical cystectomy.

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Appendix- 1

Study Proforma-

Title of the study- A prospective observational study to assess VIRADS as a diagnostic modality to differentiate between non-muscle invasive and muscle-invasive bladder cancer.

Patient's serial no.:

CR No.:

Age:

Sex:

Occupation:

Chief Complaints:

Duration of complaints:

Comorbidities:

Personal history:

Smoker and duration
Tobacco and duration

Laboratory parameter:

CBC-
RFT-
Urine routine-
Urine culture-

Radiological investigation:

Ultrasonography of Kidney, Ureter, and Bladder with post-void residual (USG KUB with post-void residual) findings:

Kidney-

Ureter-

Bladder-
(a) Number of masses
(b) Size of each mass
(c) Location of each mass
(d) Other findings

Post-void residual urine

Any other findings

mp-MRI findings:

VIRADS score:

Cystoscopy with TURBT findings:

HPE findings:

Appendix- 2

PATIENT INFORMATION SHEET

1. STUDY TITLE: - "A Cross sectional study to assess mpMRI bladder as a diagnostic modality to differentiate between non-muscle invasive and muscle invasive bladder cancer".

2. STUDY INVESTIGATORS:

Student: Dr. Sagar Yadav, Senior resident (Mch), Department of Urology.

Guide: Dr. Kumar Madhavan, Associate Professor Department of Urology

Co-Guide/s: Dr. Devashish Kaushal, Additional Professor and Head Department of Urology

Dr. Radha Sarawagi Gupta, Additional Professor Department of Radiology

Dr. Garima Goel- Professor Department of Pathology

3. Introduction:

We are conducting a research study for assessing mpMRI as a diagnostic modality for differentiating non-muscle invasive bladder cancer from muscle invasive bladder cancer before undergoing TURBT. We will compare the results with Histopathological examination reports of the same patients after TURBT to correlate with the accuracy of MRI in differentiating the two. This study is being conducted at AIIMS, Bhopal. We would like to invite you to take part in this study. If you agree to take part voluntarily, we will ask you to sign a consent form.

4. Purpose of the study:

The aim of our study is to assess assess mpMRI bladder as a diagnostic modality to differentiate between non-muscle invasive and muscle invasive

Bladder cancer.

- A bladder tumour is one of the commonest reason for hematuria (blood in urine).
- **Non-muscle invasive bladder cancers** are superficial growths in the bladder wall and can be treated cystoscopically i.e. with TURBT and installation of chemotherapy or BCG in the bladder cavity thereafter.
- **Muscle invasive bladder cancers** are cancerous growths that have gone deep down into the bladder wall or may have grown out of the bladder wall too and need more intensive treatment like radical cystectomy i.e. removal of bladder ; chemotherapy, radiation therapy).
- Bladder tumours are resected (shaved) off the bladder wall using a telescope put into your bladder through your urethra (wastepipe): TURBT (Transurethral resection of bladder tumor).
- The removed fragments of tissue are sent for pathology analysis to see whether the tumour is cancerous, and to assess how deeply the tumour has grown into the wall of your bladder.
- Some patients may need additional treatment (with chemotherapy, radiotherapy or further surgery): Muscle invasive tumors.
- Most patients need periodic follow-up with further telescopic bladder examinations.

- **What is TURBT?**

Removal of a bladder tumour (growth) from your bladder using diathermy (electrical current) or laser energy, through a telescope passed into your bladder along your urethra (water pipe) under spinal or general anaesthesia.

- Risks associated with TURBT:

1. Need for additional treatment to prevent later tumour recurrence (e.g. Mitomycin C instillation).
2. Infection in your bladder requiring antibiotic treatment.
3. Recurrence of the tumour and/or incomplete removal.
4. Delayed or ongoing bleeding requiring further surgery to remove blood clots.

5. Damage to the ureters (the tubes that drain urine for your kidneys to your bladder) requiring further treatment
6. Injury to your urethra resulting in delayed scar formation and a urethral stricture
7. Perforation of your bladder requiring a temporary bladder catheter or open surgical repair
8. Anaesthetic or cardiovascular problems possibly requiring intensive care (including chest infection, pulmonary embolus, stroke, deep vein thrombosis, heart attack and death).

- **What is mpMRI**?

Multiparametric Magnetic Resonance Imaging.

MRI is a test which uses a powerful magnet and a computer to produce detailed images of any part of the body. The MRI scanner does not use X-rays.

- Risks of MRI:

1. No short term harmful effects have been found from MRI scans. The use of magnetic fields is not thought to be harmful although long term side effects are unknown.
2. During the examination we may administer a small dose of Buscopan to ensure the cessation of peristalsis (muscle movement within the digestive system) whilst the scan is being performed.

❖ As Cystoscopy bladder tumour removal is associated with a lot of risks as compared to mpMRI, TURBT may prove to be an unnecessary step in patients who will be requiring more intensive treatment and also it may delay more definitive procedures for those in need. Although, TURBT may be a definite treatment if the diagnosis comes out to be non-muscle invasive tumour. But still they require chemotherapy installations and also the risks of recurrence or even missed out tumour on gross removal. So, regular follow up is required.

❖ In such cases, MRI may be helpful as it may help us in per-diagnosing and differentiating superficial and deep bladder wall tumors and thus guiding accordingly for the therapies

needed as bladder per the report. It will not only shorten the management time but will also help in avoiding the unnecessary morbidity to the patients done because of TURBT.

So, the purpose of our study is to assess the validity of mpMRI in discriminating the muscle invasive and non-muscle invasive bladder wall tumours so that it can prove as a non-invasive diagnostic modality in guiding treatment for patients prior to invasive modality.

5. To ensure you successfully prepare for the examination (MRI):

Every patient above the age of 64 years needs to have had a blood test within three months of their MRI examination so that their eGFR can be checked before the administration of any contrast media. If you have had your blood test performed at a GP practice outside of the Coventry area then you need to bring the eGFR result to your appointment.

6. What is gadolinium contrast medium?

- Gadolinium contrast media (sometimes called MRI contrast Media or 'dye') are chemical substances used in magnetic resonance imaging (MRI) scans. When injected into the body, gadolinium contrast medium enhances and improves the quality of the MRI images (or pictures). For example, it improves the visibility of inflammation, tumours, and blood vessels and, for some organs, blood supply. This allows a specialist doctor to examine the images and provide a written report to your doctor or specialist, to more accurately report on how your body is working and whether there is any disease or abnormality present.
- The contrast medium is injected intravenously (into a vein) as part of an MRI scan, and eliminated from the body through the kidneys.

7. If I have side effects from the gadolinium contrast medium injection, when will they occur? What can be done to treat or prevent these side effects?

- Gadolinium contrast medium is generally very safe. Side effects or reactions are uncommon, but can occur. The most common side effects of headache, nausea and dizziness occur in a small minority of patients only, but if they do occur they will be noticed within minutes of the injection.
- Less often, in approximately 1 in 1000 patients, an itchy skin rash might appear a few minutes after the injection. This appears to be due to a mild allergy. It usually settles down by itself within an hour or so, but rarely might it be a warning sign of a more serious allergic reaction developing.
- Severe allergic (anaphylactic) reactions to gadolinium contrast medium have occurred, but are extremely rare. These severe reactions, which might involve difficulty breathing and swelling of the lips and mouth, occur in approximately 1 in every 10,000 people who have gadolinium.
- Allergic reactions usually begin within several minutes of the injection, when a patient is most likely still in the scanner, or still in the radiology practice or hospital. If you have had a history of a previous allergic reaction to a gadolinium contrast injection, or a severe allergic reaction to some other material, please tell your referring doctor and/or the radiology facility where you are having the MRI, as this will affect whether a further gadolinium injection is recommended.
- **Nephrogenic systemic fibrosis (NSF)** is a rare condition associated with gadolinium contrast medium given to patients with severe renal (kidney) disease. Its onset occurs days, weeks or months after receiving gadolinium, with almost all cases occurring within 6 months of the last dose. Since radiology facilities began routinely screening patients for kidney disease, and withholding gadolinium from those with severe renal disease, NSF has become extremely uncommon. If you do have a history of kidney disease, please be sure to tell the staff at the MRI practice, so that they can check whether the disease is severe enough to mean that you should not receive gadolinium. This might involve a simple blood test of kidney function.
- Recently, it has been recognized that very small amounts of at least some forms of gadolinium contrast (about 1% of the injected dose) are retained in the tissues, mostly in

the bones, with tiny amounts in the brain. This seems to be more likely with the same forms of gadolinium contrast that have a higher risk for NSF. At this stage, there are no known adverse effects from these very small amounts of retained gadolinium. This finding has made radiologists more careful to recommend gadolinium contrast only where it is likely to assist the diagnosis.

8. Taking part - what it involves:

a. Do I have to take part?

Participation in this research is entirely voluntary. A decision to not take part, or to withdraw at any time, will not affect your rights or medical care in any way.

b. What is expected of me if I take part?

If you participate, you will have to get mpMRI done before any invasive therapeutic or diagnostic investigation. After that, Cystoscopic removal of your bladder lesion (TURBT) will be done for assessment of the stage of the tumor.

c. How long will my part in this study last?

Till the final diagnosis of bladder lesion with its stage and grade will be made.

d. What are the possible benefits in taking part?

Taking part will help in gaining knowledge about the validity of mpMRI as a diagnostic tool in assessing the bladder stage accurately. This may result in improvement of management/outcomes for you/patients like yourself.

e. What are the possible disadvantages and risks of taking part?

There are no major foreseeable disadvantages or risks because of the study. There may be risk of loss of privacy and confidentiality of information collected even though all possible measures will be taken to ensure safe data storage and access.

f. What happens to the information collected from me?

All information collected will be kept strictly confidential and not shared with anyone. Results from the study will be reported as group data and will not identify you in any way.

g. What if I change my mind regarding participation in the study?

You are entitled to change your mind and withdraw at any time during the study without any disadvantage or penalty.

h. Whom do I contact for more information or if I have further questions or concern?

If you want any information or have questions or concerns, you can contact:

Dr. Sagar Yadav **Guide**

Senior Resident (Mch) **Dr Kumar Madhavan**
Department of Urology, AIIMS Bhopal
9650217206, neelaqua74@gmail.com

It is certified that given translation to vernacular is accurate

Appendix- 3

रोगी सूचना पत्र

1. **अध्ययन शीर्षक**: गैर-मांसपेशी आक्रामक और मांसपेशी आक्रामक मूत्राशय कैंसर के बीच अंतर करने के लिए एक नैदानिक तरीके के रूप में विराड्स स्कोर का आकलन करने के लिए एक संभावित पर्यवेक्षणीय अध्ययन

2. **अध्ययन अन्वेषक:**

छात्र: डॉ. सागर यादव, सीनियर रेजिडेंट (एमसीएच), यूरोलॉजी विभाग।

मार्गदर्शन देना: डॉ कुमार माधवन , सह - प्राध्यापक, यूरोलॉजी विभाग

सह-गाइड / एस: डॉ. देवाशीष कौशल , अतिरिक्त प्रोफेसर यूरोलॉजी विभाग

डॉ. राधा गुप्ता, अतिरिक्त प्रोफेसर रेडियोलॉजी विभाग

डॉ. गरिमा गोयल, प्रोफेसर पैथोलॉजी विभाग

3. **परिचय**:

हम टीयूआरबीटी से गुजरने से पहले मांसपेशियों के इनवेसिव ब्लैडर कैंसर से गैर- गैर-मांसपेशी आक्रामक और मांसपेशी आक्रामक मूत्राशय कैंसर के बीच अंतर करने के लिए एक नैदानिक तरीके के रूप में विराड्स स्कोर का आकलन करने के लिए एक संभावित पर्यवेक्षणीय अध्ययन कर रहे हैं। हम दोनों को अलग करने के लिए एमआरआई की सटीकता के साथ सहसंबद्ध करने के लिए टीआरबीटी के बाद उन्हीं रोगियों की हिस्टोपैथोलॉजिकल परीक्षा रिपोर्ट के परिणामों की तुलना करेंगे।

यह अध्ययन एम्स, भोपाल में किया जा रहा है। हम आपको इस अध्ययन में भाग लेने के लिए आमंत्रित करना चाहते हैं। यदि आप स्वेच्छा से भाग लेने के लिए सहमत हैं, तो हम आपसे एक सहमति फॉर्म पर हस्ताक्षर करने के लिए कहेंगे।

4. **अध्ययन का उद्देश्य**:

हमारे अध्ययन का उद्देश्य- गैर-मांसपेशी आक्रामक और मांसपेशी आक्रामक मूत्राशय कैंसर के बीच अंतर करने के लिए एक नैदानिक तरीके के रूप में विराड्स स्कोर का आकलन करने के लिए एक संभावित पर्यवेक्षणीय अध्ययन

- ब्लैडर ट्यूमर हेमेटुरिया (मूत्र में रक्त) के सबसे सामान्य कारणों में से एक है।
- **गैर-मांसपेशी आक्रामक मूत्राशय के कैंसर** ऐसे कैंसर होते हैं जो मूत्राशय की दीवार में सतही वृद्धि होते हैं और सिस्टोस्कोपिक सर्जरी यानी टीयूआरबीटी या इंट्रावेसिकल थेरेपी के साथ इलाज किया जा सकता है।
- **स्नायु आक्रामक मूत्राशय के कैंसर** ऐसे कैंसर होते हैं जो मूत्राशय की दीवार में गहरे हो जाते हैं या मूत्राशय की दीवार से भी बाहर हो सकते हैं और अधिक गहन उपचार की आवश्यकता होती है जैसे कि रेडिकल सिस्टेक्टोमी यानी मूत्राशय को हटाना; कीमोथेरेपी, विकिरण चिकित्सा)।
- मूत्राशय के ट्यूमर को आपके मूत्रमार्ग (वॉटरपाइप) के माध्यम से आपके मूत्राशय में डाले गए टेलीस्कोप का उपयोग करके मूत्राशय की दीवार से हटा दिया जाता है: टीआरबीटी (ब्लैडर ट्यूमर का ट्रांसरेथ्रल रिसेक्शन)।
- ऊतक के हटाए गए टुकड़े को पैथोलॉजी विश्लेषण के लिए भेजा जाता है यह देखने के लिए कि क्या ट्यूमर कैंसर है, और यह आकलन करने के लिए कि ट्यूमर आपके मूत्राशय की दीवार में कितनी गहराई तक बढ़ गया है।
- कुछ रोगियों को अतिरिक्त उपचार की आवश्यकता हो सकती है (कीमोथेरेपी, रेडियोथेरेपी या आगे की सर्जरी के साथ): स्नायु आक्रामक ट्यूमर।
- अधिकांश रोगियों को आगे की दूरबीन मूत्राशय परीक्षाओं के साथ आवधिक अनुवर्ती की आवश्यकता होती है।

- **टीआरबीटी क्या है?**

डायथर्मी (विद्युत प्रवाह) या लेजर ऊर्जा का उपयोग करके आपके मूत्राशय से मूत्राशय के ट्यूमर (वृद्धि) को दूर करना, स्पाइनल या सामान्य संज्ञाहरण के तहत आपके मूत्रमार्ग (वाटरपाइप) के साथ आपके मूत्राशय में पारित एक टेलीस्कोप के माध्यम से।

1. टीयूआरबीटी से जुड़े जोखिम:
2. बाद में ट्यूमर की पुनरावृत्ति को रोकने के लिए अतिरिक्त उपचार की आवश्यकता (जैसे मिटोमाइसिन सी टपकाना)।
3. आपके मूत्राशय में संक्रमण के लिए एंटीबायोटिक उपचार की आवश्यकता होती है।
4. ट्यूमर की पुनरावृत्ति और/या अपूर्ण निष्कासन।
5. रक्त के थक्कों को हटाने के लिए आगे की सर्जरी की आवश्यकता वाले विलंबित या जारी रक्तस्राव।
6. मूत्रवाहिनी को नुकसान (ट्यूब जो आपके गुर्दे के लिए मूत्र को आपके मूत्राशय तक ले जाती हैं) को और उपचार की आवश्यकता होती है
7. आपके मूत्रमार्ग में चोट लगने से निशान बनने में देरी होती है और मूत्रमार्ग सख्त हो जाता है
8. आपके मूत्राशय में छेद के लिए एक अस्थायी मूत्राशय कैथेटर या खुली शल्य मरम्मत की आवश्यकता होती है
9. एनेस्थेटिक या कार्डियोवैस्कुलर समस्याओं को संभवतः गहन देखभाल की आवश्यकता होती है (छाती संक्रमण, फुफ्फुसीय एम्बोलस, स्ट्रोक, गहरी नसों की थ्रोम्बिसिस, दिल का दौरा और मृत्यु सहित)।

- **एमपीएमआरआई क्या है?**

मल्टीपैरामेट्रिक चुंबकीय अनुनाद इमेजिंग।

एमआरआई एक परीक्षण है जो शरीर के किसी भी हिस्से की विस्तृत छवियों का उत्पादन करने के लिए एक शक्तिशाली चुंबक और कंप्यूटर का उपयोग करता है। एमआरआई स्कैनर एक्स-रे का उपयोग नहीं करता है।

- एमआरआई के जोखिम:

1. एमआरआई स्कैन से कोई अल्पकालिक हानिकारक प्रभाव नहीं पाया गया है। चुंबकीय क्षेत्रों का उपयोग हानिकारक नहीं माना जाता है, हालांकि दीर्घकालिक दुष्प्रभाव अज्ञात हैं।
2. जांच के दौरान हम क्रमाकुंचन (पाचन तंत्र के भीतर मांसपेशियों की गति) की समाप्ति सुनिश्चित करने के लिए बसकोपैन की एक छोटी खुराक दे सकते हैं, जबकि स्कैन किया जा रहा है।

- ❖ चूंकि सिस्टोस्कोपी ब्लैडर ट्यूमर को हटाना एमपीएमआरआई की तुलना में बहुत अधिक जोखिमों से जुड़ा हुआ है, इसलिए टीयूआरबीटी उन रोगियों के लिए एक अनावश्यक कदम साबित हो सकता है जिन्हें अधिक गहन उपचार की आवश्यकता होगी और यह जरूरतमंद लोगों के लिए अधिक निश्चित प्रक्रियाओं में देरी भी कर सकता है। हालांकि, टीयूआरबीटी एक निश्चित उपचार हो सकता है यदि निदान गैर-मांसपेशी आक्रामक ट्यूमर हो। लेकिन फिर भी उन्हें कीमोथेरेपी इंस्टॉलेशन की आवश्यकता होती है और पुनरावृत्ति के जोखिम भी होते हैं या यहां तक कि सकल हटाने पर ट्यूमर छूट जाता है। इसलिए, नियमित अनुवर्ती कार्रवाई की आवश्यकता है।
- ❖ ऐसे मामलों में, एमआरआई मददगार हो सकता है क्योंकि यह सतही और गहरे मूत्राशय की दीवार के ट्यूमर के प्रति-निदान और अंतर करने में हमारी मदद कर सकता है और इस प्रकार रिपोर्ट के अनुसार मूत्राशय के रूप में आवश्यक उपचारों के लिए मार्गदर्शन कर सकता है। यह न केवल प्रबंधन के समय को कम करेगा बल्कि टीयूआरबीटी के कारण रोगियों को होने वाली अनावश्यक रुग्णता से बचने में भी मदद करेगा।

इसलिए, हमारे अध्ययन का उद्देश्य मांसपेशियों के इनवेसिव और गैर-मांसपेशी इनवेसिव ब्लैडर वॉल ट्यूमर में भेदभाव करने में एमपीएमआरआई की वैधता का आकलन करना है ताकि यह इनवेसिव मोडैलिटी से पहले रोगियों के लिए उपचार का मार्गदर्शन करने में एक गैर-इनवेसिव डायग्नोस्टिक मोडेलिटी के रूप में साबित हो सके।

5. यह सुनिश्चित करने के लिए कि आप परीक्षा (एमआरआई) की सफलतापूर्वक तैयारी करें:

64 वर्ष से अधिक आयु के प्रत्येक रोगी को अपनी एमआरआई परीक्षा के तीन महीने के भीतर रक्त परीक्षण करवाना चाहिए ताकि किसी भी कंट्रास्ट मीडिया के प्रशासन से पहले उनके ईजीएफआर की जांच की जा सके। यदि आपने कोवेन्ट्री क्षेत्र के बाहर जीपी अभ्यास में अपना रक्त परीक्षण किया है तो आपको अपनी नियुक्ति के लिए ईजीएफआर परिणाम लाना होगा।

6. गैडोलीनियम कंट्रास्ट माध्यम क्या है?

- गैडोलिनियम कंट्रास्ट मीडिया (कभी-कभी एमआरआई कंट्रास्ट मीडिया या 'डाई' कहा जाता है) चुंबकीय अनुनाद इमेजिंग (एमआरआई) स्कैन में इस्तेमाल होने वाले रासायनिक पदार्थ हैं। जब शरीर में इंजेक्ट किया जाता है, गैडोलीनियम कंट्रास्ट माध्यम एमआरआई छवियों (या चित्रों) की गुणवत्ता को बढ़ाता है और सुधारता है। उदाहरण के लिए, यह सूजन, ट्यूमर, रक्त वाहिकाओं और कुछ अंगों के लिए रक्त की आपूर्ति की दृश्यता में सुधार करता है। यह एक विशेषज्ञ डॉक्टर को छवियों की जांच करने और आपके डॉक्टर या विशेषज्ञ को एक लिखित रिपोर्ट प्रदान करने की अनुमति देता है, ताकि आपका शरीर कैसे काम कर रहा है और क्या कोई बीमारी या असामान्यता मौजूद है, इस बारे में अधिक सटीक रूप से रिपोर्ट कर सके।
- कंट्रास्ट माध्यम को एमआरआई स्कैन के हिस्से के रूप में अंतःशिरा (एक नस में) इंजेक्ट किया जाता है, और गुर्दे के माध्यम से शरीर से बाहर निकाल दिया जाता है।

7. अगर मुझे गैडोलीनियम कंट्रास्ट मीडियम इंजेक्शन से साइड इफेक्ट होते हैं, तो वे कब होंगे? इन दुष्प्रभावों के उपचार या रोकथाम के लिए क्या किया जा सकता है?

- गैडोलिनियम कंट्रास्ट माध्यम आमतौर पर बहुत सुरक्षित होता है। साइड इफेक्ट या प्रतिक्रियाएं असामान्य हैं, लेकिन हो सकती हैं। सिरदर्द, जी मिचलाना और चक्कर आने के सबसे आम दुष्प्रभाव बहुत कम रोगियों में होते हैं, लेकिन अगर वे होते हैं तो उन्हें इंजेक्शन के कुछ मिनटों के भीतर देखा जाएगा।

- शायद ही कभी, लगभग 1000 रोगियों में से 1 में, इंजेक्शन के कुछ मिनट बाद खुजली वाली त्वचा पर दाने दिखाई दे सकते हैं। यह एक हल्की एलर्जी के कारण प्रतीत होता है। यह आमतौर पर एक या दो घंटे के भीतर अपने आप बैठ जाता है, लेकिन शायद ही कभी यह अधिक गंभीर एलर्जी प्रतिक्रिया विकसित होने का चेतावनी संकेत हो सकता है।
- गैडोलीनियम कंट्रास्ट माध्यम से गंभीर एलर्जी (एनाफिलेक्टिक) प्रतिक्रियाएं हुई हैं, लेकिन ये अत्यंत दुर्लभ हैं। ये गंभीर प्रतिक्रियाएं, जिनमें सांस लेने में कठिनाई और होठों और मुंह में सूजन शामिल हो सकती है, गैडोलिनियम वाले प्रत्येक 10,000 लोगों में से लगभग 1 में होती है।
- एलर्जी प्रतिक्रियाएं आमतौर पर इंजेक्शन के कई मिनटों के भीतर शुरू होती हैं, जब एक मरीज अभी भी स्कैनर में है, या अभी भी रेडियोलॉजी अभ्यास या अस्पताल में है। यदि आपके पास गैडोलीनियम कंट्रास्ट इंजेक्शन के लिए पिछले एलर्जी प्रतिक्रिया का इतिहास रहा है, या किसी अन्य सामग्री के लिए गंभीर एलर्जी प्रतिक्रिया है, तो कृपया अपने रेफ़रिंग डॉक्टर और/या रेडियोलॉजी सुविधा को बताएं जहां आप एमआरआई कर रहे हैं, क्योंकि यह प्रभावित करेगा कि क्या एक और गैडोलीनियम इंजेक्शन की सिफारिश की जाती है।
- नेफ्रोजेनिक सिस्टमिक फाइब्रोसिस (NSF) गंभीर गुर्दे (गुर्दे) की बीमारी वाले रोगियों को दी जाने वाली गैडोलिनियम कंट्रास्ट माध्यम से जुड़ी एक दुर्लभ स्थिति है। इसकी शुरुआत गैडोलीनियम प्राप्त करने के दिनों, हफ्तों या महीनों के बाद होती है, जिसमें लगभग सभी मामले अंतिम खुराक के 6 महीने के भीतर होते हैं। चूंकि रेडियोलॉजी सुविधाओं ने नियमित रूप से गुर्दे की बीमारी के रोगियों की जांच शुरू कर दी है, और गंभीर गुर्दे की बीमारी वाले लोगों से गैडोलीनियम को रोकना, NSF बेहद असामान्य हो गया है। यदि आपके पास गुर्दे की बीमारी का इतिहास है, तो कृपया एमआरआई अभ्यास में कर्मचारियों को बताना सुनिश्चित करें, ताकि वे जांच कर सकें कि क्या बीमारी इतनी गंभीर है कि आपको गैडोलीनियम प्राप्त नहीं करना चाहिए। इसमें गुर्दे के कार्य का एक साधारण रक्त परीक्षण शामिल हो सकता है।
- हाल ही में, यह माना गया है कि बहुत कम मात्रा में कम से कम कुछ प्रकार के गैडोलीनियम कंट्रास्ट (इंजेक्शन की खुराक का लगभग 1%) ऊतकों में, ज्यादातर हड्डियों में, मस्तिष्क में थोड़ी मात्रा में बने रहते हैं। ऐसा लगता है कि गैडोलीनियम कंट्रास्ट के समान रूपों के साथ एनएसएफ के लिए उच्च

जोखिम है। इस स्तर पर, गैडोलीनियम की इतनी कम मात्रा से कोई ज्ञात प्रतिकूल प्रभाव नहीं है। इस खोज ने रेडियोलॉजिस्ट को गैडोलीनियम कंट्रास्ट की सिफारिश करने के लिए और अधिक सावधान कर दिया है, जहां यह निदान में सहायता करने की संभावना है।

8. भाग लेना - इसमें क्या शामिल है:

क्या मुझे भाग लेना है?

इस शोध में भागीदारी पूरी तरह से स्वैच्छिक है। भाग न लेने या किसी भी समय वापस लेने का निर्णय किसी भी तरह से आपके अधिकारों या चिकित्सा देखभाल को प्रभावित नहीं करेगा।

यदि मैं भाग लेता हूँ तो मुझसे क्या अपेक्षा की जाती है?

यदि आप भाग लेते हैं, तो आपको किसी भी आक्रामक चिकित्सीय या नैदानिक जांच से पहले एमपीएमआरआई करवाना होगा। उसके बाद, ट्यूमर के चरण के आकलन के लिए आपके मूत्राशय के घाव (टीआरबीटी) का सिस्टोस्कोपिक निष्कासन किया जाएगा।

इस अध्ययन में मेरा हिस्सा कितने समय तक चलेगा?

अंतिम निदान तक मूत्राशय के घाव का चरण और ग्रेड के साथ निदान किया जाएगा।

भाग लेने के संभावित लाभ क्या हैं?

भाग लेने से मूत्राशय की अवस्था का सटीक आकलन करने में नैदानिक उपकरण के रूप में एमपीएमआरआई की वैधता के बारे में ज्ञान प्राप्त करने में मदद मिलेगी। इससे आपके/आपके जैसे रोगियों के लिए प्रबंधन/परिणामों में सुधार हो सकता है।

भाग लेने के संभावित नुकसान और जोखिम क्या हैं?

अध्ययन की वजह से कोई बड़ा अनुमानित नुकसान या जोखिम नहीं हैं। एकत्र की गई जानकारी की गोपनीयता और गोपनीयता के नुकसान का जोखिम हो सकता है, भले ही सुरक्षित डेटा भंडारण और पहुंच सुनिश्चित करने के लिए सभी संभव उपाय किए जाएंगे।

मुझसे एकत्र की गई जानकारी का क्या होता है?

एकत्र की गई सभी सूचनाओं को कड़ाई से गोपनीय रखा जाएगा और किसी के साथ साझा नहीं किया जाएगा। अध्ययन के परिणाम समूह डेटा के रूप में रिपोर्ट किए जाएंगे और किसी भी तरह से आपकी पहचान नहीं करेंगे।

यदि मैं अध्ययन में भाग लेने के बारे में अपना विचार बदल दूं तो क्या होगा?

आप अपना विचार बदलने और अध्ययन के दौरान किसी भी समय बिना किसी नुकसान या दंड के वापस लेने के हकदार हैं।

अधिक जानकारी के लिए या यदि मेरे पास कोई और प्रश्न या चिंता है तो मैं किससे संपर्क करूं?

यदि आप कोई जानकारी चाहते हैं या आपके कोई प्रश्न या चिंताएँ हैं, तो आप संपर्क कर सकते हैं:

शोधकर्ता।

डॉ. सागर यादव.

फोन नंबर 9650217206

मुख्यमार्गदर्शक

डॉ कुमार माधवन

वरिष्ठ निवासी (एमसीएच)

यूरोलॉजी विभाग, एम्स भोपाल

neelaqua74@gmail.com

यह प्रमाणित किया जाता है कि स्थानीय भाषा में दिया गया अनुवाद सटीक है।

Appendix- 4

PARTICIPANT INFORMED CONSENT FORM (PICF)

Participant identification number for this trial: _____

Title of project- A **Cross sectional study** to assess VIRADS as a diagnostic modality to differentiate between non-muscle invasive and muscle invasive bladder cancer.

Name of Principal Investigator: Dr. Sagar Yadav (Candidate). Phone No: 9650217206

Dr. Kumar Madhavan (Chief Guide). Phone No: 9555616040

The contents of the information sheet dated _____

___ that was provided have been read carefully by me/explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks/benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

_____ Date:

(Signatures/Left Thumb impression.) Place:

Name of the Participant: _____

Son/Daughter/Spouse of: _____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

Date:

_____ Place:

Signature of the Principal Investigator

1) Witness 1 2) Witness 2

_____ _____

Signature: Signature:

Name: Name:

Address: Address:

<u>प्रतिभागी सूचित सहमति प्रपत्र (PICF)</u>

इस परीक्षण के लिए प्रतिभागी पहचान संख्या: - _____

परियोजना का शीर्षक: गैर-मांसपेशी आक्रामक और मांसपेशी आक्रामक मूत्राशय कैंसर के बीच अंतर करने के लिए एक नैदानिक तरीके के रूप में विराड्स स्कोर का आकलन करने के लिए एक संभावित पर्यवेक्षणीय अध्ययन

प्रधान अन्वेषक का नाम: डॉ. सागर यादव (उम्मीदवार)
फ़ोन क्रमांक: 9650217206
डॉ. कुमार माधवन (मुख्य मार्गदर्शक)
फोन क्रमांक: 9555616040

दिनांक_____की सूचना पत्र की सामग्री को मेरे द्वारा ध्यान से पढ़ा गया है/ मुझे विस्तार से समझाया गया है, जिस भाषा में मैं समझता हूं, और मैंने सामग्री को पूरी तरह से समझ लिया है। मैं पुष्टि करता हूं कि मुझे प्रश्न पूछने का अवसर मिला है।

अध्ययन की प्रकृति और उद्देश्य और इसके संभावित जोखिम / लाभ और अध्ययन की अपेक्षित अवधि, और अध्ययन के अन्य प्रासंगिक विवरणों के बारे में मुझे विस्तार से बताया गया है। मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मैं बिना कोई कारण बताए, मेरी चिकित्सा देखभाल या कानूनी अधिकार को प्रभावित किए बिना किसी भी समय वापस लेने के लिए स्वतंत्र हूं।

मैं समझता हूं कि इस शोध में मेरी भागीदारी से मेरे बारे में एकत्र की गई जानकारी और मेरे किसी भी मेडिकल नोट के अनुभागों को एम्स के जिम्मेदार व्यक्तियों द्वारा देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंच की अनुमति देता हूं।

मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं।

_____ दिनांक:

(हस्ताक्षर / बाएं अंगूठे का निशान) स्थान:

प्रतिभागी का नाम: _____

पुत्र /पुत्री / पति/ पत्नी: _____

पूरा डाक पता: _____

यह प्रमाणित किया जाता है कि उपरोक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।

_____ दिनांक:

प्रधान अन्वेषक के हस्ताक्षर स्थान:

१)गवाह १ २) गवाह २

_____ _____

हस्ताक्षर हस्ताक्षर

नाम: नाम:

पता: पता

Appendix-5

Letter of permission for use of VIRADS

SPECIAL TERMS

These User License Agreement Special Terms (Special Terms) are issued between **DR. SAGAR YADAV** (USER) and Copyright Clearance Centre, Inc. on the behalf of Elsevier Science & Technology Journals.

These Special Terms are in addition to any and all previous Special Terms under the User License Agreement General Terms.

These Special Terms include the terms and conditions of the User License Agreement General Terms, which are hereby incorporated by this reference as though the same was set forth in its entirety and shall beeffective as of the Special Terms Effective Date set forth herein.

All capitalized terms which are not defined herein shall have the same meanings as set forth in the User License Agreement General Terms.

These Special Terms, including all attachments and the User License Agreement General Terms contain the entire understanding of the Parties with respect to the subject matter herein and supersedes all previous agreements and undertakings with respect thereto. If the terms and conditions of these Special Terms or any attachment conflict with the terms and conditions of the User License Agreement General Terms, the terms and conditions of the User License Agreement General Terms will control, unless these Special Terms specifically acknowledge the conflict and expressly states that the conflicting term or provision found inthese Special Terms control for these Special Terms only. These Special Terms may be modified only by written agreement signed by the Parties.

1. **User information**

User name	**Sagar Yadav**
Category of User	Student
User address	Aiims campus, Bhopal, Saket nagar,Habibganj, Bhopal, 462020, Madhya pradesh, India
User VAT number	
User email	neelaqua74@gmail.com@gmail.com
User phone	9650217206
Billing information	Yadav general hospital. Opposite new telephone exchange circular road rewari Haryana.(123401) India

2. General information

Effective Date	Date of acceptance of these Special Terms by theUser: 8th JAN 2023
Expiration Date (Term)	Upon completion of the Stated Purpose
Name of User's contact in charge of the request	Sagar Yadav

3. Identification of the COA

Name of the COA	VIRADS SCORE
Author	N/A
Copyright Holder	Elsevier Science & Technology Journals
Copyright notice	Public domain. To reproduce the instrument in a publication, permission of the Journal of Urology isrequired.

4. Context of use of the COA

The User undertakes to use the COA solely in the context of the Stated Purpose as defined hereafter.

4.1 Stated Purpose

Clinical research

Title	A cross sectional study to assess VIRADS score as a diagnostic modality to differentiate between non-muscle invasive and muscle invasive bladder cancer
Study/protocol reference	
Sponsor	
Disease or condition	
Type of research	Observational
COA used as primary end point	Yes
Number of enrolled patients/subjects	•
Number of estimated failed patients/subjects	
Number of submissions of the COA for eachenrolled patient/subject	
Planned Term*	Start: 03/2023

	End: 09/2024
Mode of Administration*	Paper
If electronic administration, please indicate mode ofdata collection	
Use of IT Company (e-vendor)	No

4.2 Country and languages

Copyright Clearance Centre, Inc. on the behalf of Elsevier Science & Technology Journals grants the License to use the COA on the following countries and in the languages indicated in thetable below:

Version/Module	**Language**	**For use in the following country**
VIRADS SCORE	English	WORLDWIDE

The User understands that the countries indicated above are provided for information purposes. TheUser may use the COA in other countries than the ones indicated above.

APPENDIX-6

MASTERCHART

Age (Years)	**Gender**	**VIRADS**	**VIRADS Category**	**VIRADS Weighted score**	**Largest dimensions (cm)**	**T Stage**	**Invasion**	**Grade**	**Any Hydronephrosis**	**Hydronephrosis Laterality**	**Lesion Number**	**Number Of Lesions**
84	Male	VIRADS 1	VIRADS 1-2	1	0.75	Ta	Non-Muscle Invasive	High	Absent	None	Multiple	2
83	Male	VIRADS 4	VIRADS 3-5	4	4.7	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
80	Male	VIRADS 3	VIRADS 3-5	3	2	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
80	Male	VIRADS 4	VIRADS 3-5	4	3	T1	Non-Muscle Invasive	Low	Absent	None	Multiple	2
80	Male	VIRADS 4	VIRADS 3-5	4	2.8	T1	Non-Muscle Invasive	High	Present	Unilateral	Single	1
78	Male	VIRADS 3	VIRADS 3-5	3	1.2	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
77	Male	VIRADS 3	VIRADS 3-5	3	7.3	T1	Non-Muscle Invasive	Low	Absent	None	Single	1
75	Male	VIRADS 4	VIRADS 3-5	4	5.6	T2	Muscle Invasive	High	Absent	None	Single	1
75	Male	VIRADS 5	VIRADS 3-5	5	6	T2	Muscle Invasive	High	Present	Unilateral	Single	1
75	Male	VIRADS 5	VIRADS 3-5	5	3	T2	Muscle Invasive	High	Absent	None	Single	1
75	Male	VIRADS 5	VIRADS 3-5	5	3	T2	Muscle Invasive	High	Absent	None	Single	1
73	Male	VIRADS 5	VIRADS 3-5	5	4.8	T1	Non-Muscle Invasive	High	Absent	None	Multiple	5
73	Male	VIRADS 4	VIRADS 3-5	4	3	T1	Non-Muscle Invasive	Low	Absent	None	Single	1

72	Male	VIRADS 1	VIRADS 1-2	1	0.5	T0	Non-Muscle Invasive		Absent	None	Multiple	2
71	Male	VIRADS 5	VIRADS 3-5	5	6	T2	Muscle Invasive	High	Present	Bilateral	Single	1
70	Female	VIRADS 3	VIRADS 3-5	3	3.4	T1	Non-Muscle Invasive	Low	Absent	None	Single	1
70	Male	VIRADS 5	VIRADS 3-5	5	1.4	T2	Muscle Invasive	High	Present	Unilateral	Single	1
70	Male	VIRADS 5	VIRADS 3-5	5	10.4	T2	Muscle Invasive	High	Absent	None	Single	1
68	Male	VIRADS 5	VIRADS 3-5	5	5	T2	Muscle Invasive	High	Present	Unilateral	Single	1
66	Male	VIRADS 4	VIRADS 3-5	4	5	T1	Non-Muscle Invasive	High	Absent	None	Multiple	3
65	Female	VIRADS 2	VIRADS 1-2	2	1.8	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
65	Male	VIRADS 4	VIRADS 3-5	4	3.4	T2	Muscle Invasive	High	Absent	None	Multiple	3
65	Male	VIRADS 5	VIRADS 3-5	5	5.2	T2	Muscle Invasive	High	Absent	None	Single	1
63	Male	VIRADS 3	VIRADS 3-5	3	1.5	T1	Non-Muscle Invasive	Low	Absent	None	Single	1
63	Male	VIRADS 5	VIRADS 3-5	5	9	T2	Muscle Invasive	High	Present	Bilateral	Single	1
62	Male	VIRADS 2	VIRADS 1-2	2	5.7	T1	Non-Muscle Invasive	High	Absent	None	Single	1
61	Female	VIRADS 2	VIRADS 1-2	2	5.3	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
61	Male	VIRADS 2	VIRADS 1-2	2	3.2	T1	Non-Muscle Invasive	Low	Absent	None	Single	1
61	Male	VIRADS 2	VIRADS 1-2	2	0.6	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
61	Male	VIRADS 5	VIRADS 3-5	5	1.5	T2	Muscle Invasive	High	Present	Bilateral	Single	1
59	Male	VIRADS 4	VIRADS 3-5	4	**2.2**	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1

59	Male	VIRADS 4	VIRADS 3-5	4	5	T1	Non-Muscle Invasive	Low	Absent	None	Single	1
58	Female	VIRADS 4	VIRADS 3-5	4	4.4	T1	Non-Muscle Invasive	High	Absent	None	Single	1
58	Male	VIRADS 3	VIRADS 3-5	3	4.2	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
57	Male	VIRADS 5	VIRADS 3-5	5	6	T2	Muscle Invasive	High	Absent	None	Single	1
57	Male	VIRADS 2	VIRADS 1-2	2	1.9	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
57	Male	VIRADS 5	VIRADS 3-5	5	4.5	T2	Muscle Invasive	High	Absent	None	Single	1
56	Male	VIRADS 2	VIRADS 1-2	2	1.9	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
55	Male	VIRADS 1	VIRADS 1-2	1	0.61	Ta	Non-Muscle Invasive	Low	Absent	None	Multiple	2
55	Male	VIRADS 5	VIRADS 3-5	5	6.5	T2	Muscle Invasive	High	Absent	None	Single	1
54	Male	VIRADS 5	VIRADS 3-5	5	3	T2	Muscle Invasive	High	Present	Bilateral	Multiple	3
53	Male	VIRADS 4	VIRADS 3-5	4	6.4	T1	Non-Muscle Invasive	Low	Present	Unilateral	Multiple	2
53	Male	VIRADS 4	VIRADS 3-5	4	5.6	T2	Muscle Invasive	High	Absent	None	Multiple	3
52	Female	VIRADS 4	VIRADS 3-5	4	3.3	T2	Muscle Invasive	High	Absent	None	Multiple	4
52	Male	VIRADS 5	VIRADS 3-5	5	4.6	T2	Muscle Invasive	High	Present	Unilateral	Single	1
52	Male	VIRADS 4	VIRADS 3-5	4	**2.2**	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1
49	Male	VIRADS 5	VIRADS 3-5	5	8.4	T2	Muscle Invasive	Low	Present	Bilateral	Single	1
47	Male	VIRADS 5	VIRADS 3-5	5	3	T2	Muscle Invasive	High	Present	Bilateral	Single	1
45	Female	VIRADS 3	VIRADS 3-5	3	2.7	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1

42	Male	VIRADS 5	VIRADS 3-5	5	8.8	T2	Muscle Invasive	High	Present	Bilateral	Single	1
40	Male	VIRADS 4	VIRADS 3-5	4	1.8	T2	Muscle Invasive	High	Absent	None	Single	1
39	Female	VIRADS 4	VIRADS 3-5	4	2.8	T2	Muscle Invasive	High	Absent	None	Single	1
23	Male	VIRADS 2	VIRADS 1-2	2	1	Ta	Non-Muscle Invasive	Low	Absent	None	Single	1